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Attn: Mr. Thomas Harty

Subject: Syngenta comments to Docket ID No. EPA-HQ-OPP-2011-0581 for Thiamethoxam Registration Review

Dear Mr. Harty:

Syngenta Crop Protection, LLC herein is submitting the following comments to the Preliminary Risk Assessment for the subject docket.

Please feel free to contact me at 336-632-2446 or via email at Charles.levey@syngenta.com.

Respectfully yours,

Charles T. Levey
Federal Team Lead
Syngenta

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1.0 Executive Summary

Syngenta is providing comments to the United States Environmental Protection Agency (EPA) Memorandum for the "Preliminary Bee Risk Assessment to Support the Reregistration Review of Clothianidin and Thiamethoxam" dated January 5, 2017. Syngenta is the registrant for thiamethoxam and, therefore, our comments are specific to the risk assessment and conclusions concerning thiamethoxam. Syngenta would also like to the Agency to refer to comments submitted by the Neonicotinoid Consortium. The Neonicotinoid Consortium is made up of the four primary registrants (Bayer Crop Science, Syngenta Crop Protection LLC, Valent U.S.A. LLC and Mitsui Chemicals Agro, Inc.) of the four nitroguanidine neonicotinoid insecticides (imidacloprid, thiamethoxam, clothianidin and dinotefuran). The Consortium was formed to serve as a vehicle for collaboration on the development of protocols and generation of data to support the nitroguanidine class of neonicotinoid insecticides under registration review.

Syngenta strongly supports EPA's efforts in providing a science-based risk assessment process for thiamethoxam. Although we have considerable scientific comments on certain aspects of this assessment, we want to acknowledge that, in general, the process used by the EPA to determine risk to bees is science-based and follows a tiered approach.

It is worth noting that most uses of thiamethoxam pose low risk to bees as concluded by the Agency. Seed treatments, which comprise the majority of thiamethoxam crop use in both acreage applied and pounds used, represent low risk for bees based on very low, if any, levels of both thiamethoxam, and the degradate clothianidin, detected in pollen and nectar of seed treated crops. As stated by the Agency "given the large extent of seed treatment use of clothianidin on corn and thiamethoxam on corn, soybean and cotton, the risk conclusions indicate that the majority of pounds of clothianidin and thiamethoxam applied in the US pose a low on-field risk to honey bees" (EPA assessment, page 347). Out of the 34 use patterns evaluated for thiamethoxam, only 5 uses were found to exceed the EPA's level of concern for *nectar exposure* to thiamethoxam (Syngenta provides scientific comments on EPA's risk conclusions for *pollen exposure* as described in our Bee Bread section of this response). These 5 uses were associated with multiple foliar applications made shortly before bloom which is considered worst-case and is likely not indicative of typical use by growers for these particular crops (cotton, cranberry and cucumber). In addition, the small number of bee incidents (i.e., bee kills) cited in the preliminary risk assessment, despite the widespread use over several years, also confirms the safe use of thiamethoxam. While other crop uses were considered to pose an uncertain level of risk to bees based on a lack of pollen and nectar residue data for those crops, the lack of data does not imply risk. Syngenta is currently compiling data for 8 additional crops, including soil and foliar uses, for use by the EPA in finalizing the bee risk assessment.

Syngenta has significant scientific concerns about some of methods used in this preliminary risk assessment that were unique to this assessment (compared to the imidacloprid preliminary bee risk assessment EPA-HQ-OPP-2008-0844-0140) and outside of the methods in EPA's bee risk assessment guidance (USEPA, PMRA, CDPR 2014)[1]. These concerns are summarized in the following topics:

The use of clothianidin equivalents. EPA converted all thiamethoxam bee toxicity endpoints and residue concentrations in pollen and nectar to clothianidin equivalents given that clothianidin is a major degradate of thiamethoxam and based on the assumption that the toxicity of clothianidin and thiamethoxam are similar for bees. However, the standard toxicity studies with both terrestrial (i.e., bees) and aquatic invertebrates indicate a clear difference in chronic toxicity between clothianidin and thiamethoxam. In addition, recent laboratory chronic toxicity data show significant differences in adult bee sensitivity to thiamethoxam versus clothianidin. Considering the chronic toxicity of clothianidin to bees is *not similar* to thiamethoxam, the use of clothianidin equivalents is not appropriate. Syngenta recommends using the Toxic Unit (TU) approach to assess potential risk to individual bees consuming pollen and nectar with residues of both clothianidin and thiamethoxam and that the total TUs can be summed based on in-hive worker bees that consume the most pollen (10% of their diet) and nectar foragers that consume the most nectar (100% of their diet).

Thiamethoxam colony feeding studies. Syngenta has conducted two colony feeding studies with thiamethoxam, the first conducted in 2014-2015 and reviewed by EPA in the preliminary bee assessment, the second, a repeat study conducted in 2016-2017 that will be submitted in the next few months. Syngenta believes the 2014-2015 thiamethoxam colony feeding study was not evaluated properly by EPA, especially when compared to similar colony feeding studies for the other neonicotinoids. We provide scientific comments supporting this below showing that the performance of the thiamethoxam study was within the range of the other studies which were classified as supplemental quantitative for use in the respective risk assessments. Based on the poor overwinter survivorship in the controls, the EPA had required Syngenta and the Registrants for clothianidin to repeat the colony feeding studies. The 2016-2017 study was able to assess potential effects of thiamethoxam to colonies prior to and post winter, therefore this study should be used quantitatively in EPA's updated final ecological risk assessment.

Use of bee bread exposure in the risk assessment. Syngenta provides scientific comments on the use of EPA's bee bread calculations in determining risk to bees (see the Neonicotinoid Consortium comments for additional detail), as the intake rates are not justified based on the EPA's own BeeREX model. We note that EPA's bee bread calculations contradict the Tier 1 risk assessment assumption of increasing realism and decreasing conservatism at higher Tiers. EPA cites certain literature studies to provide support for their use of bee bread (for example

[1] USEPA, PMRA and CDPR (2014) Guidance for Assessing Pesticide Risks to Bees. Office of Pesticide Programs, United States Environmental Protection Agency, Washington, D.C.; Health Canada Pest Management Regulatory Agency Ottawa, ON, Canada California Department of Pesticide Regulation, Sacramento, CA. June 19. (available at: http://www2.epa.gov/pollinatorprotection/pollinator-risk-assessment-guidance).

Williams *et al.* 2015[2] and Sandrock *et al.* 2014[3]), however we provide extensive comments on the serious flaws of these studies.

Off-field risk assessment. EPA used the AgDRIFT model to estimate the fraction of the foliar-applied application rate at various distances beyond the treated field. The off-field risk conclusions, which are based on overly conservative assumptions concerning drift, could potentially impact the use of any foliar spray applications regardless of crop attractiveness to pollinators or agronomic practices. Syngenta recommends that the Agency consider refinements to the AgDRIFT model when supported by label language to provide a more realistic estimate of potential exposure. If available, drift deposition data from field drift studies with formulated products of the AI should be used in place of AgDRIFT estimates. In addition, if available, No Observable Effect application Rates (NOERs) from semi-field tunnels studies should be used to compare rates to the AgDRIFT deposition curve to identify distances appropriate for protecting honey bee colonies. If semi-field data are not available, the acute contact LD50 should be used in conjunction with BeeREX exposure values determined from drift deposition estimates to calculate RQs that are compared to the acute LOC. Acute oral and chronic oral risk components are not necessary as the potential area of forage that would receive drift deposition would be small compared to the forage range of honey bees and drift deposition onto pollen and nectar would be low such that potential risk from oral exposure would be minimal.

2.0 Introduction

The EPA released the preliminary bee risk assessment for clothianidin and thiamethoxam (EPA-HQ-OPP-2011-0581-0034) on January 12, 2017, and the Federal Register notice (EPA-HQ-OPP-2011-0581-0044) for public comments was published on May 25, 2017. In the preliminary bee risk assessment, EPA states that the assessment represents information that was available to the Agency and additional data are being collected and compiled and will be incorporated in an updated ecological risk assessment. The EPA has asked for public comments on the preliminary bee risk assessment including the bee bread methodology utilized in the risk assessment which represents an approach that has not been used previously in any bee risk assessment.

Thiamethoxam and clothianidin are grouped together in this assessment given that clothianidin is a major degradate of thiamethoxam, and both active ingredients have similar modes of action and use patterns. Given that Syngenta is the registrant for thiamethoxam, our comments are primarily centered on the assessment for thiamethoxam; however, clothianidin is a degradate of parent thiamethoxam and, therefore, references to clothianidin are appropriate from an exposure standpoint. We provide scientific justification against EPA's use of clothianidin equivalents in the next section, particularly as it relates to effects endpoints.

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[2] Williams, G. R.; Troxler, A.; Retschnig, G.; Roth, K.; Yanez, O.; Shutler, D.; Neumann, P.; and L. Gauthier (2015) Neonicotinoid pesticides severely affect honey bee queens. Sci. Rep. 5, 14621; doi: 10.1038/srep14621.

[3] Sandrock C, Tanadini M, Tanadini LG, Fauser-Misslin A, Potts SG and P. Neumann (2014). Impact of Chronic Neonicotinoid Exposure on Honeybee Colony Performance and Queen Supersedure. PLoS ONE 9(8): e103592. doi:10.1371/journal.pone.0103592.

The EPA, in general, followed the methodology outlined in the 2014 guidance for assessing pesticide risk to bees (USEPA, PMRA, CDPR 2014) with notable exceptions of the use of bee bread and off-site exposure which has not previously been introduced in any EPA guidance document or risk assessment. We have significant concerns about the use of these methodologies from both a scientific (e.g., unsupported food intake rates) and procedural (e.g., not appropriately vetted by a Scientific Advisory Panel) standpoints. These particular topics are more thoroughly addressed by the Neonicotinoid Consortium and summarized in the following sections of our response below.

According the EPAs preliminary risk conclusions for the 34 crop use patters assessed, the potential risk to bees in treated fields are considered:

- Low for 19 uses
- Uncertain for 10 uses
- Potentially high for 5 uses

Separated by application method:

- **Seed treatments** were preliminarily considered "low risk" for 8 crop groups and "uncertain" for 2 crop groups.
- **Soil applications** were preliminarily considered "low risk" for 4 crop groups, "uncertain" for 3 crop groups and "potentially high" for 1 crop group.
- **Foliar applications** were preliminarily considered "low risk" for 7 crop groups, "uncertain" for 5 crop groups and "potentially high" for 4 crop groups.

Many of the crops listed in EPA's preliminary low risk group were considered to be unattractive to bees or were crops that are typically harvested prior to bloom. However, several crops were considered low risk to bees even though they represent crops that are attractive (or attractive under certain conditions) to bees including seed treatments for soybean, pumpkin, canola, corn, cotton and sunflower based on very low residues detected in pollen and nectar for these seed treated crops. This is supported by several full-field colony-level studies for thiamethoxam demonstrated no colony-level effects from the use of thiamethoxam seed treatments (summarized starting on p. 189).

EPA's preliminary uncertain risk category consisted of crops that are considered attractive to bees but lack pollen and nectar residue data to help refine the exposure assessment. For many of these crop uses, including soybean (foliar), apple (foliar), citrus (foliar), pumpkin (foliar), cucurbits (soil) and strawberry (soil), additional data are being compiled and will be available for incorporation by the Agency in the updated risk assessment for pollinators prior to completion. It is important to note that lack of data does not imply risk and that the Agency should bridge data from other crops to support the conclusion of low risk to bees particularly for seed treatment uses that have shown to be of low risk based on pollen and nectar residue trials for all crops to date.

EPA's preliminary potential high risk category contained 5 uses on crops that are considered attractive to pollinators. With the exception of citrus (soil application and for pollen only), the potential risk conclusions were associated with foliar applications which can be made up to five days prior to bloom based on current labels. For two of the crop groups (stone fruit and citrus) exposure was only a concern for pollen/bee bread. As we will detail later in this response, we scientifically do not agree with EPA's approach in determining risk from bee bread exposure. Based on honey bee dietary consumption rates for pollen which is much lower than nectar, much higher concentrations in pollen are required to have an equivalent effect as seen with nectar (i.e., sugar water) exposure. When considering only nectar exposure, only 3 crops (cotton, cucumber and cranberry) represent high potential risk to bees when foliar applications are made prior to bloom. It should be noted that these conclusions are based on pollen and nectar residue trials that were conducted under worst-case exposure scenarios according to the current label in that applications were made up to 5-days prior to bloom, using the maximum allowed number of applications (typically two applications), shortest application interval (e.g., 5-7 days) and using the maximum application rate.

The preliminary risk assessment is based not only on field-derived measures of exposure from crop-specific pollen/nectar residue studies but also on effects studies, including the colony feeding studies, that may not be indicative of actual field exposures. Measured residues in pollen/nectar represent residue levels that are worst case for individual bee exposure rather than colony level exposure. In contrast, the colony feeding study represents an exposure scenario where a colony is getting the majority of its nectar from a crop over a 6-week period. Very few crops listed as potential concern by EPA would fall under this highly conservative exposure scenario where the nectar from the crop would represent the majority of nectar consumed over an extended duration. Two of the crop groups listed as high potential risk, cotton and cucurbits, are only considered moderately attractive to bees or are attractive to bees under certain conditions (USDA 2017)[4]. EPA's current bee risk assessment process does not account for attractiveness of the crop to honey bees in estimating colony level exposure (other than the crop being attractive or not attractive). Therefore, risk conclusions from this assessment represent "potential risks" to bees as noted in EPA's Executive Summary and not necessarily adverse impacts that are occurring from use of thiamethoxam under actual field conditions. Data available in the literature that include in-hive sampling (see Section 3.8 of the preliminary bee risk assessment) demonstrate a lack of widespread exposure to thiamethoxam at concentrations expected to result in colony level effects. In addition, available field and/or incident data show little evidence of colony-level effects from labeled use of neonicotinoids including thiamethoxam.

3.0 Clothianidin Equivalents

In the preliminary bee risk assessment, EPA converted all thiamethoxam bee toxicity endpoints and residue concentrations in pollen and nectar from submitted studies to clothianidin equivalents by multiplying the endpoint or exposure value by the molecular weight ratio of clothianidin to thiamethoxam (0.856). EPA's justification was that clothianidin is a major degradate of thiamethoxam and both are typically quantifiable in thiamethoxam pollen and nectar samples from residue studies, therefore a total residue approach was necessary to assess the potential risk to bees. Other reasons stated by EPA to justify this approach were that the toxicity of clothianidin and thiamethoxam are similar for bees and they have similar use patterns. While the use patterns can be considered similar, toxicity to bees, as well as other non-target

[4] USDA (2017). Attractiveness of Agricultural Crops to Pollinating Bees for the Collections of Nectar and/or Pollen. https://www.ars.usda.gov/ARSUserFiles/OPMP/Attractiveness%20of%20Agriculture%20Crops%20to%20Pollinating%20Bees%20Report-FINAL_Web%20Version_June%202017.pdf

organisms, is not similar in all instances. As stated in the thiamethoxam Problem Formulation (EPA-HQ-OPP-2011-0581-0004) "Clothianidin shows greater toxicity to aquatic invertebrates than the parent thiamethoxam" while for terrestrial organisms EPA states "Terrestrial animal toxicity data show clothianidin has demonstrated similar or less toxicity in terrestrial organisms, including honey bees, as compared to thiamethoxam". Table 1 compares the acute and chronic toxicity endpoints for bees, birds, fish and aquatic invertebrates. From an aquatic animal perspective, acute toxicity appears to be similar between the two chemicals; however, chronic toxicity endpoints are much lower for clothianidin indicating greater toxicity. For terrestrial animals, specifically birds, acute and chronic toxicity appears to be species specific; however, the lowest acute and chronic endpoint for birds is for clothianidin. For bees, while the acute toxicity to adults and larvae could be considered similar, there is a greater discrepancy in the adult and larval chronic endpoints. Adults are more sensitive to clothianidin and larvae are more sensitive to thiamethoxam albeit the chronic larval studies for thiamethoxam and clothianidin were not conducted with the same test method. It should be noted, that the chronic adult and larval toxicity study data for thiamethoxam were submitted to EPA in late 2016 and were not reviewed or incorporated into the current risk assessment and when reviewed, will add further inform the potential risk

Table 1. Ecotoxicology Data for Clothianidin and Thiamethoxam.

Study	Clothianidin[a]	Thiamethoxam[b]
Bees		
Adult honey bee acute contact	LD50 = 0.0275 μg ai/bee	LD50 = 0.0240 μg ai/bee
Adult honey bee acute oral	LD50 = 0.0037 μg ai/bee	LD50 = 0.0050 μg ai/bee
Adult honey bee chronic	10-d NOAEC = 0.00036 μg ai/bee/day	10-d NOAEC = 0.00245 μg ai/bee/day
Larval honey bee acute	8-d LC50 >15 μg ai/g-diet	8-d LC50 >3.25 μg ai/g-diet
Larval honey bee chronic	21-d NOAEC = 0.68 μg ai/g-diet	22-d NOAEC = 0.102 μg ai/g-diet
Colony feeding study	NOAEL = 19 ng ai/g	NOAEL = 50 ng ai/g (37.5 ng ai/g)[c]
Birds		
Bobwhite acute oral	LD50 > 2000 mg/kg bw/day	LD50 = 1552 mg/kg bw/day
Mallard acute oral		LD50 = 576 mg/kg bw/day
Japanese quail oral	LD50 = 423 mg/kg bw/day	
Bobwhite dietary	LC50 >5230 mg/kg diet	LC50 > 5200 mg/kg diet
Mallard dietary	LC50 > 5,040 mg/kg diet	LC50 > 5200 mg/kg diet
Bobwhite reproduction	NOAEC = 205 mg/kg diet	NOAEC = 900 mg/kg diet
Mallard reproduction	NOAEC = 525 mg/kg diet	NOAEC = 300 mg/kg diet
Fish		
Trout acute	96-hr LC50 > 101.5 mg/L	96-hr LC50 >100 mg/L
Trout chronic		NOAEC = 20 mg/L
Fathead chronic	NOAEC = 9.7 mg/L	
Aquatic invertebrates		
Daphnia acute	48-hr EC50 >119 mg/L	48-hr EC50 > 100 mg/L
Daphnia chronic	NOAEC < 0.042 mg/L	NOAEC = 100 mg/L
Chironomid acute	48-hr EC50 = 0.022 mg/L	48-hr EC50 = 0.035 mg/L
Chironomid chronic	NOAEC = 0.0011 mg/L	NOAEC = 0.010 mg/L

[a] Avian, fish and aquatic invertebrate data obtained from Registration Review: Problem Formulation Clothianidin (EPA-HQ-OPP-2011-0865-0003); Honey bee data obtained from Preliminary Bee Risk Assessment to Support the Registration of Clothianidin and Thiamethoxam (EPA-HQ-OPP-2011-0581-0034).
[b] Endpoints obtained from Syngenta submitted studies.
[c] EPA determined endpoint

The standard toxicity studies with both terrestrial (i.e., bees) and aquatic invertebrates indicate a clear difference in chronic toxicity between clothianidin and thiamethoxam. One explanation of the differences in chronic toxicity may be a result of differences in metabolism of both compounds in insects. Recent reports from the UK's Department for Environment Food and Rural Affairs (DEFRA 2014a[5]; MRID 50281202 and DEFRA 2014b[6]; MRID 50281203) indicate that although clothianidin is formed from thiamethoxam *in vivo* in bees (Figure 1; data from Table 4 in DEFRA 2014a) "half-lives for the exposure routes most relevant to foraging honey bees ranged from under one hour for oral thiamethoxam" but that the oral half-life for clothianidin is "just over five hours" (DEFRA 2014b) indicating that the two compounds have

[5] MRID 50281202 DEFRA (2014)a. Development and Improvement of Methods for the Wildlife Incident Investigation Scheme 2013-2014. Final Report PS2556.
[6] MRID 50281203 DEFRA (2014)b. Interpretation of Pesticide Residues in Honey Bees. Final Report PS2370.

very different half-lives when bees are orally exposed possibly leading to the difference in chronic toxicity observed in the laboratory adult chronic study.

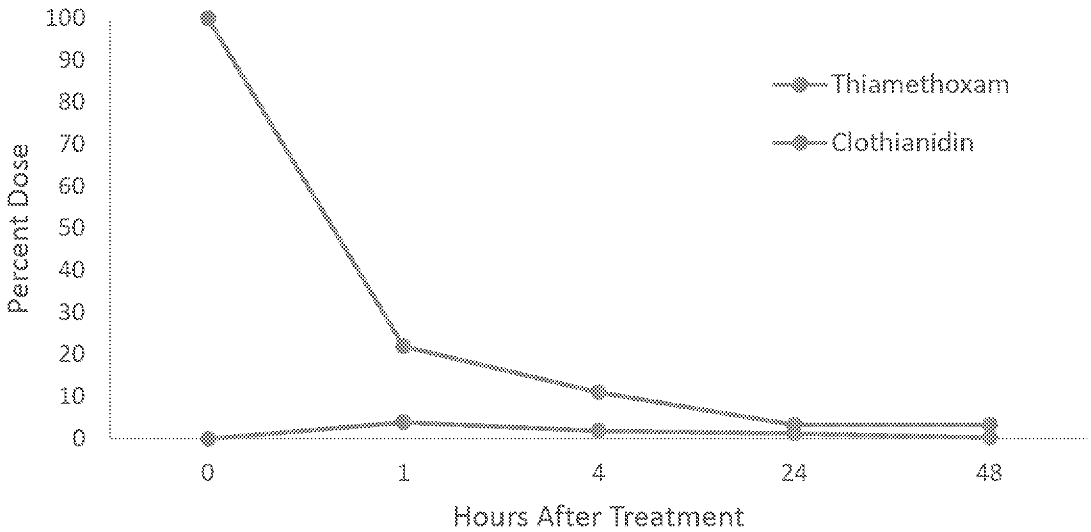

Figure 1. Residues Detect in Honey Bee Samples Dosed with Thiamethoxam (7.7 ng/bee)

Given the newly submitted laboratory chronic toxicity data show significant differences in adult bee sensitivity to thiamethoxam versus clothianidin, we believe that the Agency should not convert thiamethoxam to clothianidin equivalents. Likewise, results from the colony feeding studies show clothianidin to have a lower No Observed Adverse Effect Level (NOAEL) than thiamethoxam; this has been confirmed in four colony feeding studies, two for thiamethoxam and two for clothianidin, conducted during the same years and in the same general location (north central North Carolina). Considering the chronic toxicity of clothianidin to bees is ***not similar*** to thiamethoxam, an alternative approach to assessing the potential risk to bees from the simultaneous exposure of these chemicals through consumption of pollen and nectar that takes into consideration both exposure and toxicity needs to be implemented.

Toxic Unit (TU) approach

One method that can be used to quantify the toxicity of co-occurring compounds that may or may not have similar toxicity, but whose toxicity is considered additive, is the Toxic Unit (TU) approach. As described by von der Ohe and de Zwart (2013)[7], the TU concept has been broadly applied for the risk assessment of chemical mixtures, micro/mesocosm studies, and environmental samples (e.g. Whole Effluent Toxicity (Wet) testing). The fundamental premise of the TU approach is to scale measured compound concentrations to their inherent effect concentrations in standard test systems, which allows for relative chemical comparison and/or summation of overall effect(s). Using the TU approach potential risk to bees consuming pollen and nectar with residues of both clothianidin and thiamethoxam can be accomplished and is conceptually comparable to calculating a Risk Quotient (RQ).

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[7] Von der Ohe P and D. de Zwart (2013). Toxic Units (TU) Indicators In: Encyclopedia of Aquatic Ecotoxicology (J.F. Ferard, C. Blaise (eds.). Springer Science+Business Media Dordrecht. DOI 10.1007/978-94-007-5704-2.

Using the TU approach, potential risk to individual bees consuming pollen and nectar with residues of both clothianidin and thiamethoxam can be accomplished using the following equation:

$$\sum TU = \frac{CLO\ Nectar\ (\%\ diet) + CLO\ Pollen\ (\%\ diet)}{CLO\ NOAEL} + \frac{TMX\ Nectar\ (\%\ diet) + TMX\ Pollen\ (\%\ diet)}{TMX\ NOAEL}$$

Where: CLO Nectar = residue level of clothianidin in nectar (µg/kg)
CLO Pollen = residue level of clothianidin in pollen (µg/kg)
TMX Nectar = residue level of thiamethoxam in nectar (µg/kg)
TMX Pollen = residue level of thiamethoxam in pollen (µg/kg)
% diet = % nectar or pollen of the diet for the caste of bee
CLO NOAEL = NOAEL from clothianidin feeding study (µg/kg)
TMX NOAEL = NOAEL from thiamethoxam feeding study (µg/kg)

In this approach, the proportion of pollen and nectar consumed by different castes of bees (based on concentration using consumption values from the BeeREX model) is incorporated into the exposure value and then normalized by the NOAEL for each compound to account for the difference in toxicity of the individual compound to bees based on effects determined from the colony feeding studies. If the sum of the TUs is > 1 then the Level of Concern (LOC) for potential adverse effects is exceeded and further refinement is necessary (similar to a chronic RQ > 1). This can be used to assess potential risk on a crop-by-crop basis. To be conservative, the total TUs can be calculated based on in-hive worker bees that consume the most pollen (10% of their diet) and nectar foragers that consume the most nectar (100% of their diet). This range would cover the worst-case exposure scenarios for both pollen and nectar consumption and it is assumed all castes of bees that make up a functioning colony would fall between these two extremes.

For example, TU can be calculated using thiamethoxam and CGA322704 (clothianidin) residue data from a recently submitted pollen and nectar residue study in pumpkin where thiamethoxam treatment was made via two foliar applications at a rate of 0.086 lb ai/A (total annual rate of 0.172 lb ai/A). Maximum mean residues of thiamethoxam were 19.33 and 21.86 µg/kg for nectar and pollen, respectively; residues of CGA322704 (clothianidin) were 7.21 and 4.33 µg/kg for nectar and pollen, respectively. Using these residue values and the NOAEL (nominal concentrations) from the clothianidin and thiamethoxam colony feeding studies (50 ppb was used for thiamethoxam based on results of the 2016-2017 study) in scenarios for hive workers (maximum pollen consumption) and nectar foragers (maximum nectar consumption), the following TU calculations were made:

$$\text{(Hive workers)} \sum TU = \frac{7.21\ (90\%) + 4.33\ (10\%)}{20} + \frac{19.33\ (90\%) + 21.86\ (10\%)}{50} = 0.74$$

$$\text{(Nectar foragers)} \sum TU = \frac{7.21\ (100\%) + 4.33\ (0\%)}{20} + \frac{19.33\ (100\%) + 21.86\ (0\%)}{50} = 0.75$$

Considering both extremes of pollen and nectar consumption (i.e., hive bees and foragers) indicate the total TUs is less than 1, the potential risk for adverse effects to the colony are minimal from exposure to residues of thiamethoxam and clothianidin in pollen and nectar as a result of foliar applications made according to the label to pumpkin.

This approach can also be used to calculate TUs using pollen and nectar samples collected over time in order to determine the amount of time for total TUs to fall below the specific Level of Concern (LOC) (in this case 1) based on NOAEC or LOAEC. Figure 2 provides an example of this approach using pollen and nectar residues from pumpkin (foliar applications made prior to bloom).

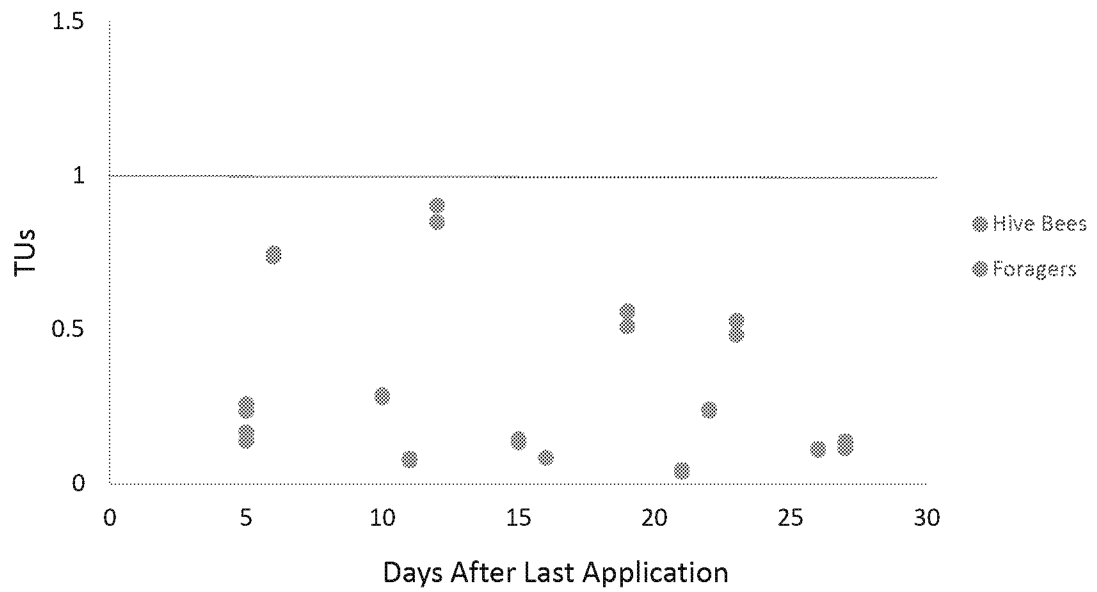


Figure 2. TUs Based on Foliar Applications to Pumpkin

4.0 Thiamethoxam Colony Feeding Study

Syngenta has conducted two colony feeding studies with thiamethoxam. The initial study was conducted in 2014-2015 and was included in the preliminary risk assessment. A repeat study was required due to the high overwinter colony mortality in all treatments and controls. The repeat study was conducted in 2016-2017 and will be submitted to the Agency in the next few months. The overall conclusions for this study are summarized as follows:

- Based on the statistically significant effects determined at the 100 ppb treatment level in several of the colony parameters measured and documented hive losses prior to winter, the Lowest Observed Adverse Effect Level (LOAEL) is 100 ppb (maximum treatment dose)
- With the exception of two time points for pollen stores (CCA5 and CCA6) at the 50 ppb treatment level, all colony parameters measured over the course of the study were similar to the controls and overwintering success exceeded the controls; therefore the data confirm that the No Observed Adverse Effect Level (NOAEL) is 50 ppb
- Considering the 2016-2017 study was able to assess potential effects of thiamethoxam to colonies prior to and post winter, Syngenta recommends that this study be used quantitatively in the updated risk assessment

The 2014-2015 thiamethoxam colony feeding study submitted to the Agency was considered to be scientifically valid but was classified as "supplemental qualitative" due to the following limitations:

1) Late timing of exposure that coincides with normal reductions in bee activity in preparation for overwintering
2) Lower than expected performance of controls
3) Lack of overwintering success

Syngenta believes the thiamethoxam colony feeding study was not evaluated similarly to the colony feeding studies for the other neonicotinoids

Comparison of the study designs for each of the four neonicotinoid colony feeding studies conducted between 2013 and 2015 are listed in Table 2. In particular, the timing of both the clothianidin and thiamethoxam studies were very similar; both were conducted during the same year (2014), same season (summer nectar dearth period), and in the same general area of North Carolina (north central part of the state). The overall study designs were reviewed and accepted by EPA, PMRA and California DPR scientists and all the registrants prior to initiation. The Agency requested that the studies start in late June/early July coinciding with the natural nectar dearth period in central North Carolina (and most of the southeastern U.S.) to avoid having the bees foraging on natural nectar sources which might lead them to avoid the provided spiked-sucrose solutions in the hive or allow for nectar to be brought back that would dilute the spiked-sucrose being fed to the colonies. Although the thiamethoxam study did start later than the other studies, it was only 13 days later than the earliest study start date which is less than a single brood cycle (21-days). Therefore, it's very unlikely that the slightly later starting time had a significant impact on the study outcome considering the consistency in control performance demonstrated below.

Table 2. Comparison of colony feeding study design details for four neonicotinoid insecticides conducted between 2013 and 2015 that have been evaluated by EPA.

	Imidacloprid[1]	Clothianidin[2]	Thiamethoxam[3]	Dinotefuran[4]
Treatment Initiation	June, 26 2013	June 26, 2014	July 8, 2014	June 29, 2015
Location	Mebane, NC	Snow Camp, NC	Mebane, NC	Mebane, NC
Randomization	Stratified	Stratified	Stratified	Stratified
Adults at CCA3	7300 adults	15,000 adults	10,000 adults	20,000 adults
Honey at CCA3	11,000 cells	45,000 cells	15,000 cells	53,000 cells
Pollen at CCA3	4,700 cells	5,700 cells	3,800 cells	7,800 cells
Brood at CCA3	23,000 cells	33,000 cells	26,000 cells	31,000 cells
Volume Treated Sucrose Solution	2 L per week (1-6)	4 L per week (1-6)	2 L per week (1-4) 3 L per week (5-6)	2 L per week (1) 3 L per week (2-6)
Number CCAs (pre, post, overwinter)	3, 4, 1	3, 4, 2	3, 5, 2	3, 5, 2

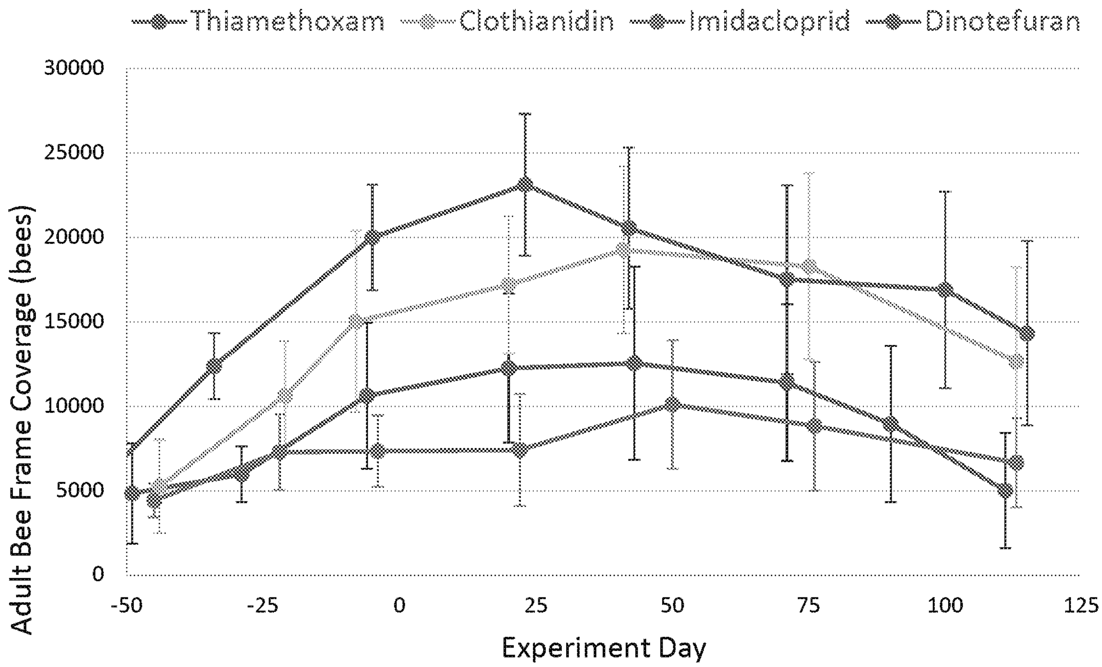
[1] Imidacloprid Colony Feeding Study Data Evaluation Record (DER): EPA-HQ-OPP-2008-0844-1033
[2] Clothianidin Colony Feeding Study DER: EPA-HQ-OPP-2011-0865-0179
[3] Thiamethoxam Colony Feeding Study DER: EPA-HQ-OPP-2011-0581-0040
[4] Dinotefuran Colony Feeding Study information provided by Mitsui Chemicals Agro, Inc. as part of the Neonicotinoid consortium

The timing of exposure is an important consideration and Syngenta asserts that exposure during the summer represents the worst case scenario for observing colony level effects. Nectar and pollen sources are very abundant during the spring in the Southeast U.S. Feeding treated solution during this time would result in significant dilution. In addition, given the availability of nectar and pollen resources available in the landscape during spring, foraging bees would only need to forage over a small distance to acquire adequate resources for colony expansion and reproduction (i.e., swarming). In contrast, in areas where nectar sources are less abundant in the summer (e.g., southeast and many other regions of the U.S.), honey bee foraging distances increase significantly during the summer in order to meet the needs of a colony whose population has expanded significantly during the spring. A recent study (Couvillon, Schurch and Ratneiks 2014)[8] found that "as bees will not forage at long distances unnecessarily, this suggest summer is the most challenging season, with bees utilizing an area 22 and 6 times greater than spring or autumn." This is particularly important given that the most consistent effect noted in the neonicotinoid colony feeding studies is reduced pollen stores likely associated with a reduction in foraging or reduced forage efficiency. Therefore, exposure during summer would be the most likely time frame for detecting this apparent treatment related effect as foraging during summer would require greater effort than either spring or fall.

[8] Couvillon M, Schurch R, and Ratnieks F. (2014). Waggle Dance Distances as Integrative Indicators of Seasonal Foraging Challenges. PLoS ONE 9(4): e93495. Doi:10.1371/journal.pone.0093495

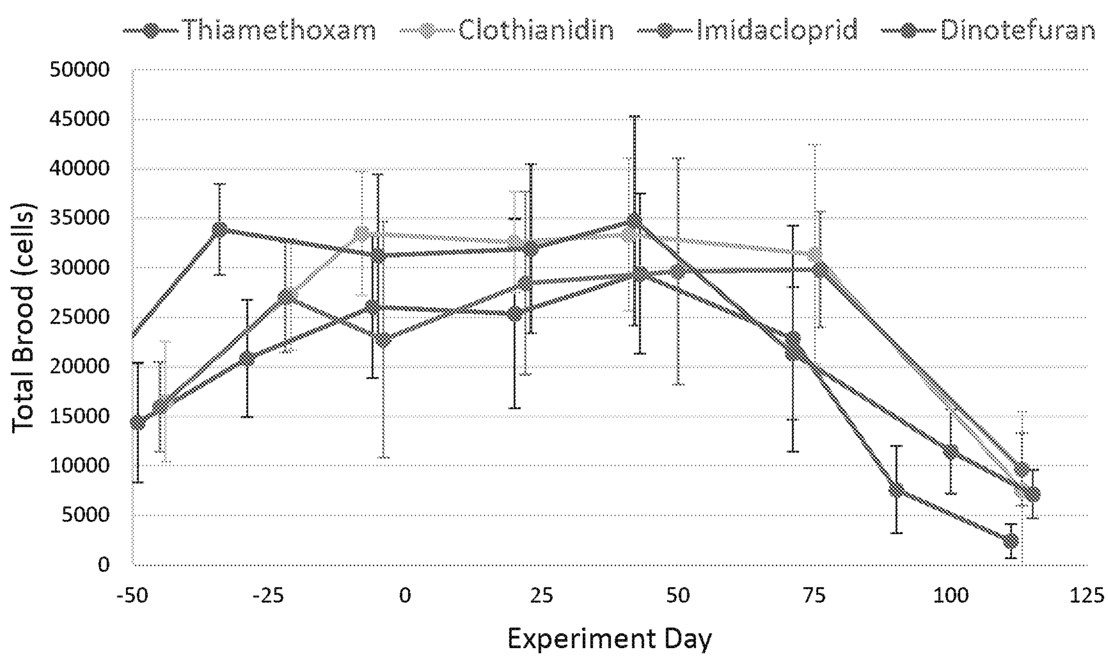
Colony sizes at the start of treatment were different between the studies based on the preference of the CRO conducting the study. However, the volume of treated sucrose fed to the colonies was in proportion to the overall colony size. There was some uncertainty by both the Agency and the Registrants on what size the colonies should be and the appropriate volume of treated solution to feed. There was concern that feeding too much treated sucrose solution could result in back filling the brood box which could result in inadequate space for the queen to lay eggs and, thus, encouraging swarming. The desire was to feed the amount of sugar to meet the needs of the colony and to insure consumption of the treated sugar solution as opposed to over feeding and having the colonies store the excess solution as honey which would not increase exposure but simply extend the exposure over a longer duration. EPA also commented that the quantity of treated sugar solution fed to the colonies likely did not fulfill the complete carbohydrate needs of the colony but did not provide any reference or analysis to support that point other than to mention there was a lack of remaining sucrose solution during renewal at some of the test concentrations. However, it is important to note that removal of sucrose solutions from feeders is not an indication of consumption as honey bees will conveniently store excess nectar (or sugar water) within the colony for later use (i.e., honey stores).

Lower than expected control performance was also identified as a weakness of the study and a reason for downgrading the study to "supplemental qualitative". When comparing the data evaluation records (DERs) for both the clothianidin and thiamethoxam colony feeding studies, the reviewers had very similar criticisms for control performance in both studies (Thiamethoxam Colony Feeding Study DER: EPA-HQ-OPP-2011-0581-0040; Clothianidin Colony Feeding Study DER: EPA-HQ-OPP-2011-0865-0179), yet these "limitations" did not result in a downgraded study for clothianidin. Comparing the control performance across the four colony feeding studies indicate that the performance was within the range of the other studies which were classified as acceptable for use in the respective risk assessments (Figures 3 and 4). Figure 3 shows that while each of the colony feeding studies started out with different numbers of bees, the overall pattern of growth was similar with the control colonies continuing to grow during the exposure phase, in which the colonies were receiving treated sucrose solution (untreated for controls), and then subsequent reductions in adult numbers post treatment as a result of the lack of additional feeding which also coincided with the time of the year when colonies begin preparations for winter. Likewise, a similar pattern is also seen in total brood coverage, which includes eggs, larvae and capped brood (Figure 4). Overall, the control datasets show that control colonies behaved very similarly in all four colony feeding studies and that this pattern of growth is typical for honey bee colonies in the Southeast U.S. or, essentially, any other temperate region where most of the nectar production (i.e., honey flow) occurs in the spring, followed by a dearth in nectar production in the summer, and then a slight, but inconsistent, increase in nectar production in the fall where colonies decrease in size and store honey (if surplus nectar is available in the Fall or via supplemental feeding) in preparation for winter.



Error Bars = 1 standard deviation of control mean

Figure 3. Comparison of Adult Bees Control data for the Four Colony Feeding Studies (2013-2015).



Error Bars = 1 standard deviation of control mean

Figure 4. Comparison of Total Brood Control data for the Four Colony Feeding Studies (2013-2015)

Control performance could potentially have been better in both the clothianidin and thiamethoxam studies if supplemental feeding of the colonies were allowed after the exposure period. The bee experts conducting both the thiamethoxam and clothianidin studies were concerned that within weeks after the exposure period, nectar and honey stores were too low and that there was not enough nectar forage in the landscape to maintain sufficient food stores and adult numbers to levels that would support successful overwintering. Feeding the colonies sucrose solution at this time (late summer/fall) is a normal beekeeping practice for the area of the US where the study took place, particularly for first year colonies started from packages. However, EPA advised that the colonies should not be fed supplemental sucrose until after the last CCA of the season to avoid any potential dilution of the test substance that might be stored in the hives. Although feeding was allowed to be initiated after the last CCA (end of October), the timing coincided with the first frost which did not provide sufficient time to get the honey stores built up (honey bees need adequate time to evaporate water or "ripen" the honey); at least 40 lbs. of honey are needed for storage) and adult numbers were below the number required for an adequate cluster size which ultimately led to the poor overwintering survival.

Lack of overwinter success was an obvious weakness for both the clothianidin and thiamethoxam studies. This was likely a result of several factors including the lack of honey stores and small cluster size mentioned above. However, it is possible that the control colonies could have had better survival if the winter was milder, similar to what was observed for the imidacloprid study (2013-2014). However, colony losses in the control were high (>50%) by late December 2014 and in February/March 2015 there was a prolonged period of cold weather that resulted in high losses across all treatments and control particularly in those colonies that had initiated brood production. Based on the poor overwinter survivorship in the controls, the EPA had asked Syngenta and the Registrants for clothianidin to repeat the colony feeding studies in 2016. Final reports for these studies are currently being prepared and preliminary results have been presented to the Agency. Overall, effects noted in the 2016 study are very similar to the 2014 study in that statistically significant effects were observed in pollen stores, larvae, pupae and total brood coverage at the highest treatment concentration (100 ppb) which can be considered treatment related. With the exception of two time points for pollen stores (CCA3 and CCA4) at the 50 ppb treatment concentration, all colony parameters measured over the course of the study, including overwintering success, were similar to the controls; therefore the data confirm that the No Observed Adverse Effect Concentration (NOAEC) is 50 ppb. Based on the statistically significant effects determined at the 100 ppb treatment level in several of the colony parameters measured and documented hive losses prior to winter, the Lowest Observed Adverse Effect Concentration (LOAEC) is 100 ppb (maximum treatment dose). Overall, overwinter hive losses ranged between 8.3 and 25% with the highest losses at the highest treatment rate (25% at 100 ppb). Considering the 2016-2017 study was able to assess potential effects of thiamethoxam to colonies prior to and post winter (and confirmed effects noted in the previous study), Syngenta recommends that this study be used quantitatively in the updated final ecological risk assessment.

5.0 Bee Bread use in the Risk Assessment

The EPA has asked for public comments on the bee bread methodology used in the risk assessment. The method was implemented in the clothianidin and thiamethoxam preliminary bee risk assessment without prior notification or guidance. Syngenta has significant scientific concerns about this methodology as presented below (see the Neonicotinoid Consortium comments for more detail). We also provide critiques of the two pollen exposure papers cited by EPA (Sandrock *et al.* 2014 and Williams *et al.* 2015) as these papers suggest that residues in pollen/bee bread can result in colony level effects at lower concentrations than residues in nectar. This contradicts what is known about pollen and nectar consumption rates for both individual honey bees and colonies, fails to address total consumption of residue by bees via pollen and nectar and violates the assumptions of the Tiered risk assessment approach as developed by USEPA, PMRA and CDPR and after a Science Advisory Panel review, was adopted by EPA.

Syngenta agrees with the Neonicotinoid Consortium comments concerning the use of EPA's bee bread calculations in determining risk to bees which are summarized below (see the consortium comments for additional detail):

- A significant challenge concerning exposure to bees in that the matrix used in the effects studies (sucrose, royal jelly) differs from the exposure endpoints (nectar and pollen) and that there is a need to determine total residue consumption from multiple dietary items (i.e., pollen and nectar) similar to how dietary exposure is assessment for other organisms (e.g., bird omnivores).
- Based on consumption rates for all life stages and castes of the honey bee, pollen and nectar should not be considered equally potent on a concentration basis. Given that all life stages of honey bees consume much more nectar than pollen, total dietary exposure should be greatly weighted toward residue concentrations in nectar versus pollen. Nectar is also mixed with pollen to form bee bread which provides an additional route of dietary intake for nectar.
- Bayer Crop Science has conducted pilot colony feeding trials with imidacloprid which confirm that there is a much greater colony response to exposure via nectar compared to pollen which is supported by the intake rates used in the BeeREX model.
- However, the EPA assumed that the response of the colonies in the colony feeding studies are due to bee bread dietary exposure alone even though these studies were designed to expose the bees to treated sugar solution and that the primary route of exposure is from consumption of the sugar solution which is supported by known intake rates for honey bees.
- Overall, based on BeeREX intake rates converted to bee bread dosages (see consortium comments for table), bee bread represents only a small percentage (~17%) of the total dose adult bees ingest (for in-hive bees while foragers consume 0%). Therefore, the consortium proposes an alternative approach that converts pollen concentrations to a "nectar equivalent" by dividing by 5 which is conservatively based on the fact that hive bees consume approximately 5-10 times more nectar than pollen and that total hive consumption of nectar to pollen is at least 5:1 but likely higher.
- Additionally, there is an apparent error in the equation used by EPA to calculate bee bread concentrations that overestimates concentrations by about 60%.

The Agency referenced two studies from the open literature (Williams *et al.* 2015 and Sandrock *et al.* 2014) that indicate bee bread spiked with clothianidin and thiamethoxam can effect honey bee colonies. However, these studies are scientifically flawed and should not be used in the risk assessment for the following reasons.

The Williams *et al.* (2015) study is not directly comparable to any of the other colony feeding studies as it evaluated colonies set up for mass rearing of queens which involves very different colony management practices. The condition of the queens may have been impacted by the exclusion of collected pollen in the treated colonies equipped with pollen traps. The effect reported by Williams *et al.* (queen failure) has not been found to occur in field studies (e.g., Cutler *et al.* 2014, Rundloff *et al.* 2015) of conventionally-managed colonies or by commercial beekeepers. The Williams et al. study was also a small study (6 test colonies of which 3 received pesticide treatment) that employed pseudo-replication in the experimental design. It should be dismissed as unsuitable for use in risk assessment.

The Sandrock *et al.* (2014) study reported a small difference in colony strength endpoints immediately after the exposure period (short-term impact), but subsequently recovered and overwintered successfully. However, there was a significant difference between treatment and control colonies the following summer for which there is no explanation from a toxicological perspective. It is clear that the bees were not being exposed at the time these colony failures occurred, but it's not clear if they were ever exposed at any time during their development or as adults particularly given that no detectable residues of either clothianidin or thiamethoxam were reported in adult bees, pupae, pollen, honey, bee bread or wax, during the study, in spite of a limit of detection of 0.1 ppb.

The absence of residues in all matrices could illustrate an avoidance of the spiked pollen which was, unfortunately, not explored by Sandrock *et al.* (2014). One possibility is that the bees were avoiding the spiked pollen and the effects noted were the result of a lack of pollen available to raise brood which would give similar results noted in the colony feeding studies (decreased pollen stores and brood). The study authors also noted that the pollen coverage increased post treatment from 17.9 dm^2 to 29.8 dm^2 in the control (66% increase) and from 20.8 dm^2 to 24.9 dm^2 (20% increase) in the treated, suggesting an effect on pollen storing that continued once the pollen traps were removed with normal pollen collection reduced by 50% (compared to the control) which could reflect lower brood levels and lack of demand for pollen. The challenge is that pollen availability affects brood production (in the absence of sufficient pollen, larvae are cannibalized) and brood presence affects pollen collection so there are knock-on effects if brood levels are reduced and colonies build up slower. The unusual effect (from a toxicological standpoint) in the delayed build-up the following spring could be related to the nutritional impact on the colony (from pollen trapping) compared to the control the previous summer/autumn.

Another significant weakness of the Sandrock *et al.* (2014) study is that only a single exposure level was tested and it is not clear if the results would follow a dose-response gradient. In addition, the study looked at only 2 groups of 12 hives each at a single location with the two groups only separated by 20 m. The Agency considered the study "robust" with 12 replicates (i.e., hives) even though individual hives should not be considered replicates (i.e., pseudo-replicates) and the statistical analysis is unusual in that the study authors used days as an independent factor. In contrast, the Registrant submitted colony feeding studies had a total of 12 true replicates (i.e., 12 apiaries), demonstrated a robust dose-response relationship (using 5 treatments and a control), were consistent in effects observed across the neonicotinoid active ingredients (imidacloprid, clothianidin and thiamethoxam), and results were replicated over two separate years (for clothianidin and thiamethoxam) – all of which are significant strengths of the registrant-submitted colony feeding studies.

6.0 Assessment of Pollinator Risk from Off-Field Drift

To assess the potential risk to bees exposed to thiamethoxam or clothianidin drift in off-field habitat, EPA used the BeeREX model (v.1.0) to determine risk quotients (RQs) for acute contact and oral and chronic oral exposure routes based on foliar application rates. The level of concern (LOC), which is 0.4 for acute and 1.0 for chronic, divided by the RQ determined the drift fractions that would be acceptable such that the RQ was less than the LOC for acute and chronic exposure. The drift fraction was then used with the AgDRIFT® model (v. 2.1.1) to estimate the distance at which acceptable drift deposition would occur for ground and aerial applications. The distance required for the drift fraction to be low enough such that the RQ no longer exceeded the acute or chronic LOC for acute contact and oral as well as chronic oral scenarios was determined as stated in Table 5.5 of the preliminary risk assessment. It is important to note that this method was not a component of the bee risk assessment process that was vetted with the Scientific Advisory Panel (SAP) and is not part of the formal bee risk assessment guidance (US EPA, PMRA, CDPR 2014).

Syngenta agrees with the Neonicotinoid Consortium comments concerning the off-field assessment method in determining risk to bees which are summarized below (see the Consortium comments for additional detail):

- Any spray buffers that might be recommended based on off-field assessments are not necessary based on current pollinator protection goals and given the fact that label language is already in place that prohibits the drift of thiamethoxam and clothianidin to flowering crops and weeds with instructions to minimize the availability of blooming plants prior to application. Thus prior to and during application, measures need to be taken that will minimize any off-field exposure and potential risk to bees foraging in off-field field habitats.

- The off-field assessment method uses conservative default values as inputs to the AgDRIFT model which can be refined based on label specific language. Additional aspects, pointed out by the Agency in the assessment, that likely lead to overestimation of exposure are that the model assumes there is no interception by the crop canopy and that winds are unidirectional and constant to the off-field area.

- The method uses Tier I laboratory-based effects endpoints (acute oral and contact LD50; chronic oral NOED) to determine acceptable drift deposition distances. A more realistic approach would be to use No Observed Adverse Effect Rates (NOAER) from Tier II semi-field tunnel studies, if available, and compare those rates to the AgDRIFT deposition curve to identify distances equivalent to the NOER that would protect the colony.

- Off-field spray drift is predominantly composed of the smallest droplet sizes (driftable fines) that do not deposit on plant structures (i.e. leaves, stems, flowers) in the same fashion as a direct, saturating overspray due to the nature of atmospheric mechanisms impacting the dispersion of airborne particles and their interaction with solid surfaces.

- The proposed EPA method incorporates both contact and oral exposure routes over both acute and chronic exposure durations. From a dietary standpoint, the amount of drift that could potentially land on pollen and/or nectar is likely much lower compared to what could potentially land on leaf material. Off-field habitat immediately adjacent to a crop where a thiamethoxam or clothianidin foliar application was made and the proportion of the habitat where spray drift actually deposited on the plants, taking into consideration plant interception, is likely small and would not be a significant portion of the overall feeding range of the colony foragers. The chronic endpoint is also based on a continuous oral exposure even though degradation, based on available pollen and nectar residue studies, can be substantial.

- Given the number of overly conservative assumptions concerning both the route and duration of exposure for off-field drift to bees, the acute and chronic dietary component should be removed and if any off-field assessment is needed, the focus should be on assessing the potential risk to bees from acute contact exposure to spray drift.

- Recommendations are that the Agency should consider refinements to the AgDRIFT model when supported by label language to provide the best estimate of potential exposure considering the drift deposition estimates are highly conservative. If available, NOAERs from semi-field tunnels studies should be used to compare rates to the AgDRIFT deposition curve to identify distances appropriate for protecting honey bee colonies. If semi-field data are not available, the acute contact LD50 should be used in conjunction with BeeREX and AgDRIFT to determine acceptable distances such that acute LOCs are not exceeded. Acute oral and chronic oral risk components are not necessary as the potential area of forage that would receive drift deposition would be small compared to the forage range of honey bees and drift deposition onto pollen and nectar would be low such that potential risk from oral exposure would be minimal.

7.0 Incident Reports and Other Lines of Evidence

The EPA considers other relevant information, such as reported incidents involving bees, in their preliminary bee risk assessment for clothianidin and thiamethoxam. The Agency cites twenty-one incidents involving honey bees reported in the U.S., from 2002-2015, associated with agricultural uses of thiamethoxam. Seven incidents have been reported in association with corn planting in Indiana, Minnesota and Illinois. As mentioned in the report, exposure of bees to clothianidin and thiamethoxam via drift of abraded seed coat dust is considered a route of concern, but “the Agency is working with different stake holders to identify best management practices and to promote technology-based solutions that reduce this potential route of exposure.” Minimizing dust drift resulting from planting treated seed is among the highest priorities for Syngenta. Examples of our extensive efforts in this regard include our ongoing efforts to develop and optimize new seed treatment formulations and tank-mix recipes to minimize dust abrasion through the use of new and improved dust reducing agents and polymers. In addition, at our new, state-of-the-art Syngenta Seedcare Institute, we provide extensive applicator training to our seedcare customers, including seed companies and treaters, on how to properly handle, and apply, our products during seed treatment. Further, we offer technical assistance to these same customers at their treatment sites when questions and/or issues arise to ensure our seed treatment products are properly applied. Through our sales and seed advisor staff, we educate growers on the best way to handle and plant treated seed to minimize dust abrasion and dust-off at planting as well as disposing leftover treated seed properly. Syngenta also conducts extensive research in seed treatment application technology to determine the best seed processing steps (i.e., cleaning seed before treatment to remove seed generated dust) all the way to evaluating and optimizing droplet/particle sizes during seed treatment application to ensure our products stay on the seed while handling and planting to minimize dust-off.

Out of the remaining incidents reported, twelve were reported by the State of Washington in 2002 with applications to orchards where honey bee hives were located within the orchards, although it is unclear whether these were separate incidents or involved the same beekeeper. One incident was reported in California in association with thiamethoxam applications to lemon trees and the final incident was associated with an application to "an agricultural area". It is unclear whether these incidents were associated with off-label use (i.e., misuse) which is an important consideration as applications are not allowed during bloom or when bees are foraging within the treated area and any direct application to a hive would be considered a label violation. Current labels for products containing thiamethoxam are very clear concerning the hazard to bees and that applications to blooming crops or weeds are prohibited. Overall, the number of incidents appears to be quite low given the extent of use of thiamethoxam in the U.S. over the 17 years it's been registered in the U.S. which is a testament to the safe use of thiamethoxam products by growers and the continued stewardship provided by Syngenta.

While incident data generally involves obvious effects on honey bees (i.e., bee kill), additional lines of evidence indicate low risk to bees include potential impact to honey bee colonies from current labeled uses of thiamethoxam. Several field studies have been conducted (summarized in Table 4.32 of the preliminary risk assessment), primarily in Europe, on thiamethoxam use as a seed treatment showing no impacts on honey bee colonies. As stated by the Agency, "all lines of evidence taken together suggest impacts to honey bees are not expected on field for seed treatment for corn and canola." Additional field studies including various orchard crops have also been submitted to PMRA and have not been formally evaluated by EPA, but should provide additional lines of evidence concerning the general lack of effects to honey bee colonies when thiamethoxam is applied according to the approved label

8.0 Comments/Corrections

Preliminary Bee Risk Assessment to Support the Registration Review of Clothianidin and Thiamethoxam

The following specific comments are provided with respect to the Preliminary Bee Risk Assessment to Support the Registration Review of Clothianidin and Thiamethoxam (Docket ID: EPA-HQ-OPP-2011-0581-0034).

Docket ID:	EPA-HQ-OPP-2011-0581-0034
Section Title:	1. Executive Summary

Paragraph: Page No.: Comment No.:	1 5 of 414 1
EPA Statement	*These two chemicals are assessed together because 1) clothianidin is a degradate of thiamethoxam; 2) the toxic effects and the concentrations at which they occur at for these two chemicals are similar for bees; and, 3) their use patterns are similar. Clothianidin is observed as a major degradate of thiamethoxam in many fate studies, including pollen and nectar residue studies. Therefore, a total residue approach is necessary to assess the potential risks of thiamethoxam to bees.*

Syngenta Comments:

Syngenta agrees that both thiamethoxam and clothianidin should be assessed together from an exposure perspective, but disagrees that the toxic effects on bees is similar for both chemicals. As previously noted in these comments, the chronic toxicity of clothianidin to bees (either at an individual or colony level) is **not similar** to thiamethoxam and, therefore, the use of clothianidin equivalents is not appropriate. Syngenta recommends either simply adding residues of both thiamethoxam and clothianidin (i.e., total residues) and comparing to the thiamethoxam effects endpoints or, more conservatively, using the Toxic Unit (TU) approach to assess potential risk to individual bees consuming pollen and nectar with residues of both clothianidin and thiamethoxam and that the total TUs can be summed based on in-hive worker bees that consume the most pollen (10% of their diet) and nectar foragers that consume the most nectar (100% of their diet).

In addition, although use patterns for thiamethoxam and clothianidin are similar, applications rates are not with single maximum foliar application rates generally higher (approximately 2x) for clothianidin than those for thiamethoxam (p. 6 under Use Profile).

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary 2 5 of 412 2
EPA Statement	*Clothianidin and thiamethoxam are xylem and phloem- mobile systemic compounds in plants and are readily taken up by the roots of the plant and translocated throughout the plant via the transpiration stream.*

Syngenta Comments:

Thiamethoxam is a systemic compound and moves within the xylem of the plant however Syngenta disagrees with the Agency's statement that thiamethoxam is also phloem-mobile. A study by Daniels (2008)[9] (MRID 50281201) investigated the movement of several compounds in wheat after application of radio-labeled material to the leaf surface. As can be seen in Figure 5, radio-labeled sucrose, which is both xylem- and phloem-mobile, is detected not only in the leaf where the application was made (1st leaf) but also in the 2nd and 3rd leaf as well as the roots of the wheat plant. However, wheat treated with radio-labeled thiamethoxam is primarily only observed in the treated leaf with minimal detection in the 2nd and 3rd leaf and no detection in the roots (Figure 6).

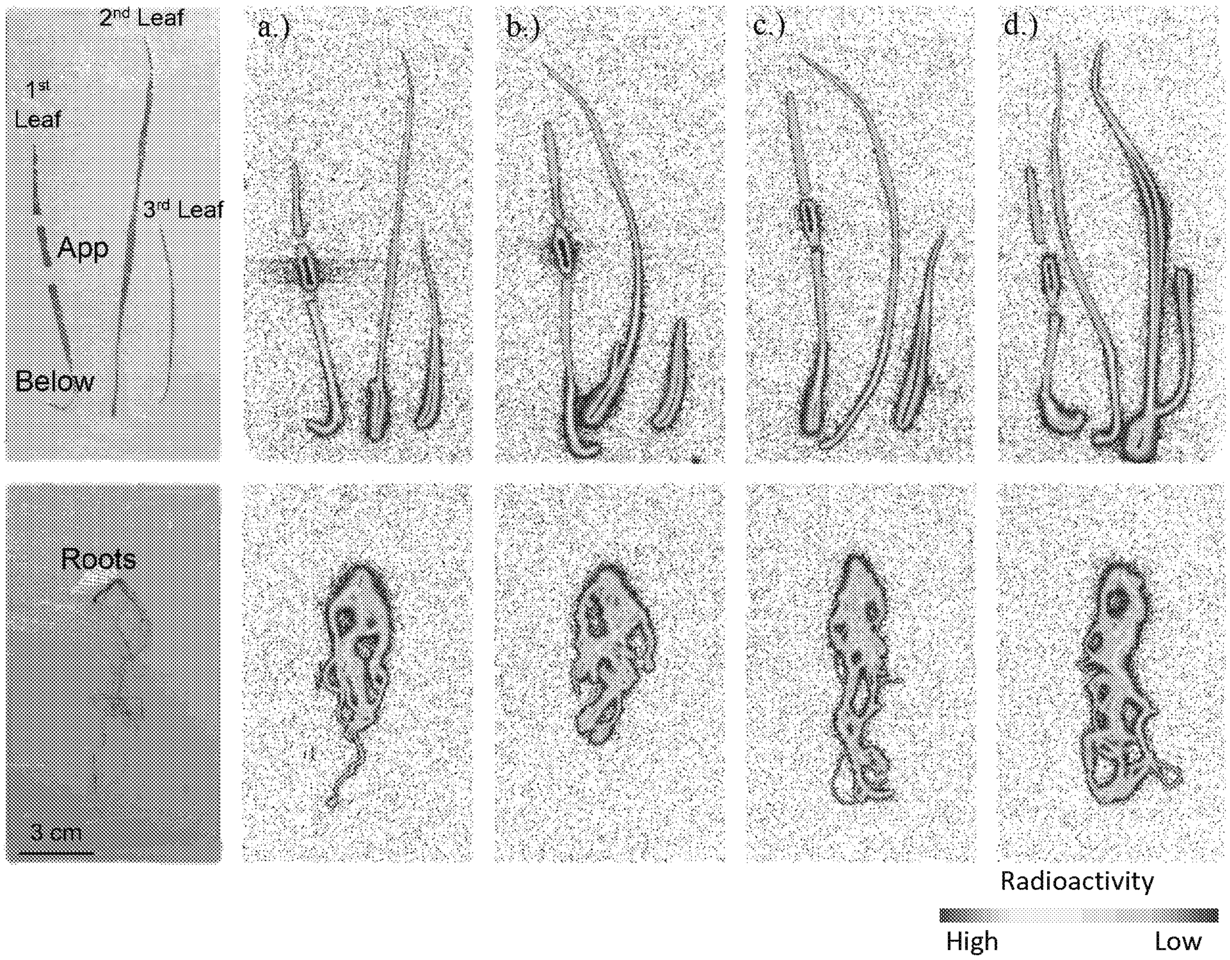


Figure 5: Phosphor images showing the distribution of ^{14}C a.) 2 h, b.) 8 h, c.) 24 h and d.) 72 h after a leaf application of [^{14}C]-sucrose to wheat. (From Daniels 2008)

[9] MRID 50281201. Daniels, M. 2008. Investigating the uptake and translocation of thiamethoxam (and other xenobiotics) in wheat (*Triticum aestivum* L.) and its effects on the bird cherry-oat aphid (*Rhopalosiphum padi* L.). Ph.D. dissertation. University of Birmingham. 289 p.

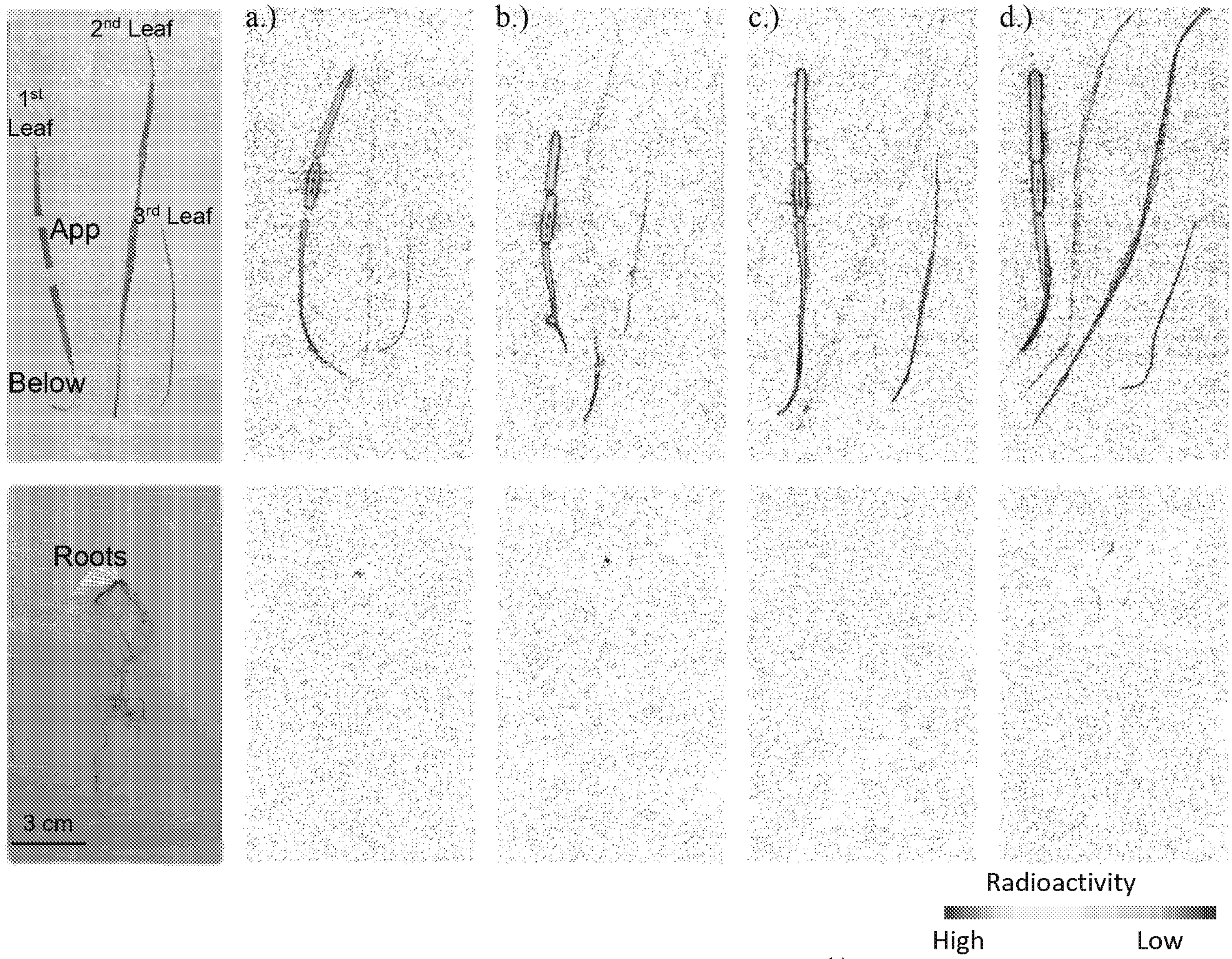


Figure 6: Phosphor images showing the distribution of ^{14}C a.) 2 h, b.) 8 h, c.) 24 h and d.) 72 h after a leaf application of [^{14}C]-thiamethoxam to wheat. (From Daniels 2008)

In addition, aphids, which are known to feed on phloem sap, were allowed to feed on the treated wheat plants and phloem samples were collected from their stylus. Both sucrose and glyphosate, which are phloem mobile, were detected in the phloem sap and showed increasing levels over time. However thiamethoxam, pymetrozine and the control, which are not phloem mobile, were not detected in the phloem sap over time (Figure 7).

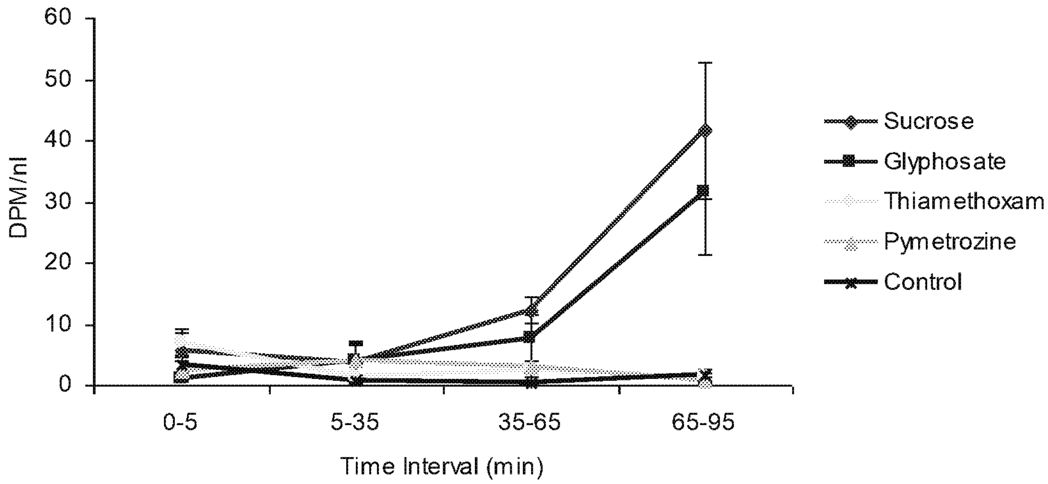


Figure 7: Presence of radioactivity in phloem sap collected using aphid stylectomy from wheat treated with radiolabelled compound (0.12 MBq). Stylectomy was performed on apterous *R. padi* feeding on the stem region of 10-day old wheat plants. Plants were treated with [^{14}C]-compound (0.12 MBq) 10 cm above the exuding stylet on the 1st leaf, 5 minutes after the start of exudation. Graph represents mean DPM/nl ± SEM (n = 4). (From Daniels 2008).

Furthermore, analysis of the honeydew from the aphids feeding on the treated wheat leaves showed detection of sucrose and glyphosate but no detection of thiamethoxam, pymetrozine or the control confirming that the phloem-mobile compounds were being ingested and excreted while the non-phloem-mobile compounds were not ingested and not found in the excreted honeydew.

Overall, this study provides several lines of evidence that thiamethoxam is not phloem-mobile and should only be characterized as a systemic, xylem-mobile insecticide.

Docket ID:	EPA-HQ-OPP-2011-0581-0034
Section Title:	1. Executive Summary
Paragraph:	1
Page No.:	6 of 412
Comment No.:	3
EPA Statement	*With regards to the bee bread component, it should be noted this a newly developed method in an effort to evaluate potential risks from contaminated pollen which is not considered at Tier II when comparing the sucrose (nectar)-based exposure toxicity data with nectar residue concentrations. This methodology was developed in collaboration with PMRA and CDPR, and is being considered as a qualitative additional line of evidence in evaluating potential risk.*

Syngenta Comments:

We appreciate the Agencies determination that this new bee bread methodology will be only considered as "qualitative" in the risk assessment as an additional line of evidence in evaluating potential risk. However, Syngenta and the Neonicotinoid Consortium have significant concerns about this methodology as previously described in these comments and recommend that the Agency discontinue this methodology and use a more scientifically defensible method that incorporates both pollen and nectar consumption of various bee life stages or for the colony as a whole. Both Syngenta and the Neonicotinoid Consortium provide examples for summing pollen and nectar dietary components together to derive the total dietary concentration.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary Table 1.1 8 of 412 4
EPA Statement	*Table 1.1* *Cotton*

Syngenta Comments:

The cotton residue values for pollen, nectar and extra floral nectar presented in Table 1.1 do not match the data from the cotton study (MRID 49686801) or data points presented in Figure 5.36

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary Table 1.1 8 of 412 5
EPA Statement	*FL Citrus and CA Citrus footnote*[a] [a] = Some trials in this study were conducted at different applications. All concentrations were normalized to the maximum single application rate of 0.172 lb a.i./acre.

Syngenta Comments:

Normalizing the citrus pollen and nectar residue data to 0.172 lb ai/acre (maximum soil application rate) assumes that the residues detected in pollen and nectar is linearly correlated with application rate. For soil applications, other variables including soil type and characteristics, rainfall, timing of application, and tree density also have an influence on measured residues in both pollen and nectar. Therefore, without a verification of a linear relationship between application rates and the residues detected, the residue data should not be normalized to a single rate and only data for the maximum application rate (0.172 lb ai/acre) or lower used in the assessment.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary Table 1.1 8 of 412 6
EPA Statement	*Table 1.1 Canola* a = highest atypical clothianidin value (759 ppb) excluded. Next highest value (46.89 ppb) presented. Max and mean value are identical because there was only a single sampling interval.

Syngenta Comments:

The canola study cited (MRID 49819502) was designed to determine if soil applications to potato would carry over to pollen and nectar residues in thiamethoxam seed treated canola. Canola grown from untreated seed in plots that were treated the previous year with a soil application of thiamethoxam had similar pollen residues to canola grown from treated seed. The untreated controls also had similar pollen residues levels which suggests that the pollen residue levels may not be the result of the thiamethoxam seed treatments. In addition, there was only one sampling interval for the study and, therefore, a chronic EEC based on multiple sampling intervals cannot be used. Given the uncertainty in this study, pollen and nectar residue data from separate canola study (MRID 49775702) should be used in the refined assessment.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary 1 9 of 412 7
EPA Statement	*When considering seed treatment data, the BeeREX default value of 1000 ng c.e./g is consistently 1-2 orders of magnitude above residues measured in pollen and nectar. This suggests that BeeREX overestimates exposure for seed treatments and therefore may be overly protective.*

Syngenta Comments:

Syngenta encourages the Agency to continue to compare BeeREX estimated environmental concentrations (EECs) to actual measured residues in pollen and nectar. We also agree that the BeeREX default value of 1 ppm for seed treatments is overly protective and recommend that this estimate be revised to a more realistic value.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary 2 9 of 412 8
EPA Statement	*Data considered suitable for deriving acute risk quotients for adult honey bees are available for both chemicals; however, such data are only available for clothianidin for chronic exposures to adults and acute and chronic exposures to larvae. Given that the Tier I data set is complete for clothianidin and that the available data indicate that thiamethoxam and clothianidin are of similar toxicity, the clothianidin toxicity endpoints are used to assess risk.*

Syngenta Comments:

Syngenta submitted chronic toxicity data for both adult honey bees (MRID 50084901)[10] and larvae (MRID 50096607)[11]. The chronic 10-day NOAEL for adult bees was 0.00245 µg ai/bee/day which is an order of magnitude higher (i.e., lower toxicity) than the clothianidin endpoint (10-day NOAEL = 0.00036 µg ai/bee/day). A 22-day chronic larval study for thiamethoxam was also submitted to the Agency which resulted in a NOAEC of 0.102 µg ai/g-diet which is lower than the clothianidin endpoint however different test methods were used which might have influenced the results. The data, particularly for adult bees, indicate that the toxicity of thiamethoxam and clothianidin to bees are **not similar**, at least from a chronic exposure perspective. As previously discussed, when assessing toxicity of both thiamethoxam and clothianidin combined, a toxic unit approach would be considered appropriate given that the differences in chronic toxicity particularly to adult bees which represent the most sensitive life stage.

[10] MRID 50084901. Kling A. (2016) Thiamethoxam – Assessment of Effects on the Adult Honey Bee, *Apis mellifera* L., in a 10 Day Chronic Feeding Test under Laboratory Conditions. Unpublished study by Eurofins Agroscience Services EcoChem GmbH.

[11] MRID 50096607. Eckert J. (2016) Thiamethoxam – Honey Bee (*Apis mellifera* L.) Larval Toxicity Test (Repeated Exposure through to Adult Emergence). Unpublished study by Eurofins Agroscience Services EcoChem GmbH.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary 3 10 of 412 9
EPA Statement	*Similar effects, including a decline in the number of adult females (workers) and pollen stores followed by a decline in brood (eggs, larvae, and pupae), were observed across the two CFS studies (Table 1.3). Often, the declines in brood were observed weeks after the impacts to workers were observed. This suggests that the impacts on brood were not likely a direct effect, but rather a colony response to a decline in number of workers and/or pollen reserves.*

Syngenta Comments:

Reductions in foragers were not significant until the second Colony Condition Assessment (CCA) for thiamethoxam (and other neonicotinoid CFS with the exception of clothianidin at the highest concentration) with reductions in pollen stores and brood occurring during the first and second CCA after treatment. Although it is uncertain whether the reduction in pollen stores occurred prior to reduction in brood, a possible explanation is that there was a treatment related effect on foraging or foraging efficiency which resulted in reduction in pollen stores. Reduced pollen stores could result in reduction in the number of brood present in the colonies. This appears to be the most likely scenario given the higher larval toxicity endpoint values which suggests that direct impacts to larvae are less likely.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary 3 10-11 of 412 10
EPA Statement	*It is noted that neither CFS study had a successful overwintering component due to poor control survival during overwintering. This creates uncertainty surrounding the endpoint used in the risk assessment, as there is potential that colonies in treated groups that had experienced effects could have recovered following the winter period, or, alternatively, colonies not exhibiting effects prior to over wintering could exhibit adverse effects after winter. Additionally, given other study deficiencies in the thiamethoxam CFS, the clothianidin CFS was the primary study used to evaluate potential colony-level effects. When evaluating residue data in nectar for clothianidin, the no observed effect concentration (NOEC) was 19 ng c.e./g and lowest observed effects concentration (LOEC) was 35.6 ng c.e./g. These effect concentrations from the clothianidin CFS are consistent with the effect concentrations from the thiamethoxam CFS.*

Syngenta Comments:

As previously stated in this document, Syngenta recommends that the 2016-2017 thiamethoxam colony feeding study be used quantitatively in the updated ecological risk assessment however we also believe the deficiencies noted by the Agency for the 2014-2015 colony feeding study are unfounded and believe that the Agency unfairly evaluated the study. We also disagree that the effects concentration from the clothianidin colony feeding study are consistent with the effect concentrations from either thiamethoxam colony feeding study. For example, reduction in the number of adult bees were noted at the three highest concentrations (40, 80 and 160 µg/L) for the clothianidin colony feeding study while effects on adults bees were only noted for the highest concentration (100 µg/L) in both thiamethoxam colony feeding studies. The number of adult bees can be considered a direct measure of overall colony strength. While significant differences were also noted for other endpoints during thiamethoxam exposure at the 50 µg/L concentration, these were transient and endpoints were similar to controls prior to winter. In addition, overwinter colony survival at the 50 µg/L concentration in the 2016-2017 study was higher than the controls confirming this concentration as the NOAEC for thiamethoxam.

Docket ID:	EPA-HQ-OPP-2011-0581-0034
Section Title:	1. Executive Summary
Paragraph:	2
Page No.:	11 of 412
Comment No.:	11
EPA Statement	*An additional line of evidence to characterize potential colony-level effects was potential exposure through bee bread. For the clothianidin CFS, the lowest observed adverse effects concentration (LOAEC = 35.6 ng c.e./g-sucrose) had 95% confidence interval concentrations of 8.6-15.7 ng c.e./g-bee bread (mean concentration of 12.2 ng c.e./g). Additionally, there were two open literature studies (Williams et al. 2015 and Sandrock et al. 2014)) which evaluated colony level effects through an exposure route similar to bee bread (pollen paddies consisting of pollen and sucrose source). Effects similar to the two CFS studies (e.g., decreased adults/pollen stores/brood) were also observed in these two studies at comparable, but slightly lower, bee bread concentrations from the clothianidin CFS. While the clothianidin CFS was used as the primary study for this line of evidence, these open literature studies were used as additional characterization.*

Syngenta Comments:

As mentioned previously, EPA's conclusion is based on the assumption the response of the colonies in the CFSs are due to bee bread dietary exposure alone even though the CFSs were designed to expose the bees to treated sugar solution and that the primary route of exposure is from consumption of the sugar solution which is supported by known intake rates for honey bees. The two open literature studies (Williams *et al.* 2015 and Sandrock *et al.* 2014) which appeared to showed similar effects but at lower concentrations in spiked bee bread are seriously flawed (single dose studies with pseudo-replicates) and should not be used in the risk assessment. In contrast, the Registrant submitted colony feeding studies had a total of 12 true replicates (i.e., 12 apiaries), demonstrated a robust dose-response relationship (using 5 treatments and a control), were consistent in effects observed across the neonicotinoid active ingredients (imidacloprid, clothianidin and thiamethoxam), and results were replicated over two separate years (for clothianidin and thiamethoxam).

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 1. Executive Summary Table 1.5 19-24 of 412 12
EPA Statement	*See Table 1.5*

Syngenta Comments:

A couple of errors were noted:

1) On page 19 for Fruiting Vegetables both foliar and soil applications, it states that "Crop group generally does not produce honey bee attractive pollen and nectar[b]", without a reference to the footnote at the bottom of the table.
2) On page 20 for Legume Vegetables/foliar application the individual bee (Tier 1) risk concern "Yes" or "No" designation is missing.
3) Page 23 in the row for Cotton the Tier II risk concern is "Yes-Nectar" which appears to be correct only for extra floral nectar and not floral nectar.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 2.4 Overview of Uses Tables 2.1 and 2.2 and throughout 28-31 of 412 13
EPA Statement	*Single app rate (lb a.i./A)* *(clothianidin equivalent)*

Syngenta Comments:

We appreciate that the Agency is likely using clothianidin equivalents to compare application rates between clothianidin and thiamethoxam. However, presenting the single application rate as clothianidin equivalents gives the impression that efficacy is directly related to the presence of clothianidin rather than the parent thiamethoxam. In general, residue detections of clothianidin are much lower than parent thiamethoxam in crops (including crop pollen and nectar). In addition, as mentioned by the Agency, maximum foliar application rates tend to be lower for thiamethoxam than clothianidin which are determined by efficacy on target insect pests.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 2.4 Overview of Uses Table 2.3 32-33 of 412 14
EPA Statement	*Table 2.3. Seed treatment uses and corresponding application rates registered for clothianidin and thiamethoxam.*

Syngenta Comments:

Syngenta identified some possible errors in the calculation of the seed application rates for the following crops in Table 2.3:

1) For Crop Group 3 **Onion**, thiamethoxam is only registered on dry bulb onion.
2) In the row for **Lettuce**, Syngenta calculated the rate to be 2.7E-06 lb a.i./seed.
3) For **Soybeans**, Syngenta calculated the rate to be 1.0E-03 lb a.i./seed.
4) Syngenta calculates the rate for **Peas** to be 5.0E-04 lb a.i./lb seed.
5) For **Corn (field)**, Syngenta calculates the rate as 2.8E-06 lb a.i./seed and 5.0E-03 lb a.i./lb seed.
6) For **Corn (pop)**, Syngenta calculates the rate as 2.8E-06 lb a.i./seed and 1.1E-02 lb a.i./lb seed.
7) For **Corn (sweet)**, Syngenta calculates the rate as 2.8E-06 lb a.i./seed and 8.8E-03 lb a.i./lb seed.
8) **Alfalfa** rate was calculated by Syngenta to be 2.4E-09 lb a.i./seed based on 210,000 alfalfa seeds/lb.
9) Syngenta calculates the **Peanut** rate as 5.4E-04 lb a.i./lb seed.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 2.5 Overview of Physicochemical, Fate, and Transport Properties 2 36 of 412 15
EPA Statement	*Clothianidin and thiamethoxam are considered xylem mobile, with dominant uptake routes following the transpiration stream (i.e., no downward transport from leaves to roots). Although xylem mobile, numerous field studies have demonstrated that clothianidin and thiamethoxam applied via foliar, soil or seed treatment methods can result in residues in pollen and nectar of blooming plants indicating that they are phloem mobile as well.*

Syngenta Comments:

As previously mentioned, thiamethoxam is xylem mobile but not phloem mobile. Detection of thiamethoxam and clothianidin in pollen and nectar when applied via soil and seed treatment methods demonstrate that these compounds are **xylem mobile**. Detections in pollen and nectar from foliar applications are likely the result of flower bud material being sprayed directly prior to bloom rather than movement of thiamethoxam from leaf to flower tissue (see previous discussion).

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 2.6 Stressors of Toxicological Concern 2 37 of 412 16
EPA Statement	*It is assumed that thiamethoxam and clothianidin are of similar toxicity to bees. This is supported by available toxicity data (discussed in Section 4).* *• Because toxicity data are available for clothianidin for the full suite of Tier I studies (including acute and chronic toxicity data for adults and larvae) but are only available on adult acute toxicity for thiamethoxam, clothianidin toxicity endpoints are used to generate RQs for both clothianidin and thiamethoxam.* *• Because the clothianidin colony feeding study is considered more reliable, the no observed adverse effect concentration (NOAEC) from the clothianidin colony feeding study will be used in both the clothianidin and the thiamethoxam tier II assessments.*

Syngenta Comments:

As previously discussed, new Tier I laboratory data demonstrate that the chronic toxicity of thiamethoxam is much lower for adult bees than clothianidin. Therefore, Tier I endpoints should be used separately in the assessment or a toxic unit approach can be used to compare toxicity of different mixtures of thiamethoxam and clothianidin. We also disagree with the assertion that the clothianidin CFS is more reliable. The Agency should refer to the 2016-2017 thiamethoxam colony feeding study for determining a thiamethoxam-specific NOAEC in the updated risk assessment.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 3.1.2 Physical, chemical, fate and transport properties - Thiamethoxam 4 56-60 of 412 17
EPA Statement	*3.1.2 Physical, chemical, fate and transport properties - Thiamethoxam*

Syngenta Comments:

Syngenta has previously provided comments on the environmental fate of thiamethoxam during the Problem Formulation comment phase. Please refer to those comments for recommended corrections (EPA-HQ-OPP-2011-0581-0025).

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 3.5 Tier I (default) exposure estimation Multiple tables starting with Table 3.10 69-70 of 412 18
EPA Statement	*Multiple tables with "Max. Single Appl. Rate (lbs c.e./A)"*

Syngenta Comments:

The maximum foliar single application rate for thiamethoxam is 0.086 lbs ai/A which is equivalent to 0.074 lbs c.e./A.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 3.6 Refined exposure characterization Equation 1 73 of 412 19
EPA Statement	*See Equation 1*

Syngenta Comments:

Equation 1 appears to have an error. For example, if you input in a concentration of 0 for pollen and 10 for nectar you will get a bee bread concentration that is higher (11.25) than the concentration in nectar. Also, if you input 10 for pollen and 10 for nectar the result does not come out to be 10 as expected but 15.8. The Neonicotinoid Consortium provided additional details on this apparent error that overestimates bee bread concentrations and provides options to correct the error. However, correcting this error would not alleviate our concerns about the "bee bread approach" as previously addressed in these comments.

Docket ID:	EPA-HQ-OPP-2011-0581-0034
Section Title:	4.1.1 Sources of Data
Paragraph:	Bottom of page
Page No.:	121-122 of 412
Comment No.:	20
EPA Statement	*...no quantitative Tier I data are available for chronic exposures of thiamethoxam (either for adults or larvae).* *Table 4.1. Comparison of most sensitive quantitative endpoints used in the screening-level and refined Tier I risk estimation for clothianidin and thiamethoxam (converted to clothianidin equivalents).*

Syngenta Comments:

Syngenta submitted the following studies to the Agency including chronic toxicity data for both honey bee adults and larvae.

Study Type	Thiamethoxam Endpoint	MRID No.
Adult Chronic Oral Toxicity	10-day NOAEL / LOAEL (mortality): 0.00245 / 0.00485 µg ai/bee/day 10-day NOAEC / LOAEC (mortality): 0.117 / 0.211 mg ai/kg-diet	50084901[12]
Larval Chronic (repeat dose)	22-day NOAEL/LOAEL (emergence): 0.0157 / 0.0313 µg ai/bee/day 22-day NOAEC/LOAEC (emergence): 0.102 / 0.203 mg ai/kg-diet	50096607[13]

[12] MRID 50084901. Kling A. (2016) Thiamethoxam – Assessment of Effects on the Adult Honey Bee, *Apis mellifera* L., in a 10 Day Chronic Feeding Test under Laboratory Conditions. Unpublished study by Eurofins Agroscience Services EcoChem GmbH.

[13] MRID 50096607. Eckert J. (2016) Thiamethoxam – Honey Bee (*Apis mellifera* L.) Larval Toxicity Test (Repeated Exposure through to Adult Emergence). Unpublished study by Eurofins Agroscience Services EcoChem GmbH.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 2.6 Stressors of Toxicological Concern Table 4.12 135 of 412 21
EPA Statement	*Table 4.12. Tier I acute contact toxicity data for adult honey bees (Apis mellifera) (48-h study duration).*

Syngenta Comments:

The first study listed (Actara®) in Table 4.12 has the same MRID as the second study even though they are not the same study. In addition, it is unclear how the indirect contact endpoint was derived for the first study cited. For the second study in the table, the acute contact toxicity endpoint for the Cruiser® 250 dust study are based on g ai/ha and not µg ai/bee.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 2.6 Stressors of Toxicological Concern Table 4.16 137 of 412 22
EPA Statement	*Table 4.16. Tier I acute oral toxicity data for adult honey bees (Apis mellifera) (48-h study duration).*

Syngenta Comments:

Syngenta has no record of the study listed in bold (MRID 49005702). The Tier I acute oral endpoint should be based on the previously accepted TGAI study (MRID 44714927)

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 4.2.1.2 Open Literature Studies 4-6 147-148 of 412 23
EPA Statement	*There were two Tier II studies evaluated from the open literature to characterize the colony-level effects of clothianidin to honey bees. These studies were similar to the registrant-submitted feeding study in that they had multiple replicates (i.e. hives) per treatment and monitored colony strength and development.* *In the first study by Williams et al. 2015…* *In the other study by Sandrock et al. 2014b…*

Syngenta Comments:

The two literature studies cited (Williams *et al*., 2015 and Sandrock *et al.,* 2014) are not appropriate for use in the risk assessment. Both these studies are only similar to the registrant-submitted feeding studies in that the study authors looked at colony level effects (although Williams *et al.* 2015 only used nuclear colonies managed for queen production). Neither study had true replicates (separate apiaries) or multiple test concentrations. In contrast, the Registrant submitted colony feeding studies had a total of 12 true replicates (i.e., 12 apiaries), demonstrated a robust dose-response relationship (using 5 treatments and a control), were consistent in effects observed across the neonicotinoid active ingredients (imidacloprid, clothianidin and thiamethoxam), and results were replicated over two separate years (for clothianidin and thiamethoxam) – all of which are significant strengths of the registrant-submitted colony feeding studies. In addition, the registrant submitted colony feeding studies exposed colonies to treated sugar solution representing nectar since, as stated by the Agency (p.48), ingestion of pesticide residues in nectar likely represents the predominant route of exposure for bees.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 4.2.2.1 Registrant submissions – Colony Feeding Study 3 163 of 412 24
EPA Statement	*Ten Colony Condition Assessments (CCAs) were conducted during the study. Two CCAs (CCA1 - 2) were conducted prior to feeding (i.e., pre-exposure phase) to determine hive strength (number of adult and developing bees) and initial hive conditions, CCAs 3-5 were conducted during the exposure phase, CCAs 6-8 were conducted post exposure and CCA9-10 were conducted after overwintering.*

Syngenta Comments:

Correction: Three CCAs (CCA1 – 3) were conducted prior to exposure and two CCAs (CCAs 4 and 5) were conducted during the exposure phase.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.1.2 Tier I – Screening-level RQs (On-field Oral) 3 203 of 412 25
EPA Statement	*Also as noted previously, the quantitative chronic oral toxicity study for honey bee larvae exposed to clothianidin (MRID 48876801) was unable to determine a dose-based endpoint. Therefore, chronic risk to honey bee larvae was assessed using the model-generated exposure values in pollen and nectar directly compared to the dietary-based NOAEC from the chronic honey bee larval study.*

Syngenta Comments:

As previously mentioned, the larval chronic (22-day) study for thiamethoxam has been submitted to the Agency.

Syngenta also recommends using dietary-based endpoints (LC_{50} and NOAEC) from the larval toxicity studies as the dose is based on a cumulative exposure and a daily dose cannot be estimated from these studies since diet is not completely consumed until the end of the larval phase (and if food is still present it is noted in the study report). Other reasons we recommend using concentrations for the larval endpoints include: 1) consumption by the larvae is exponential during the growth phase and only food consumption for 5-day old larvae is considered in the risk assessment, 2) the consumption rates for laboratory larvae should be similar to larvae in the field (hives), and 3) endpoints can be compared directly with pollen and nectar residue concentrations.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.1.2 Tier I – Screening-level RQs (On-field Oral) Table 5.4 205 of 412 26
EPA Statement	*Table 5.4. Summary of acute and chronic risk quotients (RQ) for adult bees from seed treatment applications of clothianidin and thiamethoxam (screening-level oral on-field)*

Syngenta Comments:

Correction: The Tier I EEC for pollen and nectar is 1 µg c.e./g (ppm) for seed treatments. The table and text below has 1 µg c.e./kg (ppb). The RQ calculations are correct.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.2.1.1 Clothianidin – Foliar Applications Last paragraph 209 of 412 27
EPA Statement	*As depicted in Figure 7, all the RQs are below their respective LOCs with the single exception of an adult chronic RQ exceeding the LOC.*

Syngenta Comments:

Correction: The figure cited should be 5.1.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.2.2.1 Thiamethoxam – Foliar Applications Table 5.34 238 of 412 28
EPA Statement	*Table 5.34. Summary of Tier I Oral RQs for Adult Honey Bees Using Refined Exposure Estimates based on Total Measured Thiamethoxam Residues in Pollen and Nectar from Foliar Applications to Cucumber1,4*

Syngenta Comments:

The "Chronic Exposure" and "Chronic RQ" values in Table 5.34 appear to be incorrect based on the reported Chronic EECs. However, the data points in Figure 5.10 appear to be correct.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.2.2.3 Thiamethoxam – Seed Treatments Table 5.49 254-55 of 412 29
EPA Statement	*Table 5.49. Summary of the Refined Acute and Chronic Estimated Environmental Concentrations for Seed Treatments on Canola Based on Measured Residue Data*

Syngenta Comments:

As previously mentioned, the canola study cited (MRID 49819502) was designed to determine if soil applications to potato would carry over to pollen and nectar residues in thiamethoxam seed treated canola. Canola grown from untreated seed in plots that were treated the previous year with a soil application of thiamethoxam had similar pollen residues to canola grown from treated seed. In addition the untreated controls had similar pollen residue levels which suggests that the pollen residue levels may not be the result of the thiamethoxam seed treatments. In addition, there was only one sampling interval and, therefore, a chronic EEC based on multiple sampling intervals cannot be used. Given the uncertainty in this study, pollen and nectar residue data from a separate canola study (MRID 49775702) should be used to derive the EECs for canola.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.2.2.3 Thiamethoxam – Seed Treatments Table 5.52 256-257 of 412 30
EPA Statement	*Table 5.52. Summary of Tier I Oral RQs for Honey Bees Using Refined Exposure Estimates Based on Measured Total Thiamethoxam Residues in Pollen and Nectar from Seed-Treated Cotton*

Syngenta Comments:

The Acute RQs appear to be calculated incorrectly and should be similar to the chronic RQs

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.3.2 Chronic Table 5.55 261-62 of 412 31
EPA Statement	*Table 5.55. Summary of the maximum mean clothianidin and total thiamethoxam residue concentration (in terms of clothianidin equivalents) in pollen and/or nectar from the residue studies and the chronic oral larval toxicity values for honey bees (all values in unit of ng/g-diet)*

Syngenta Comments:

It should be noted that Larval Endpoint #3 came from a study (MRID 48448803) that was categorized as "Supplement Qualitative".

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.5 Tier II analysis for *Apis* sp. Table 5.57 267 of 412 32
EPA Statement	*Table 5.57. Colony-level toxicity data relevant to bee bread exposure. Concentrations represent exposure levels where effects to hives were observed.*

Syngenta Comments:

As previously discussed in the "Bee Bread" section of our comments, the Agency should not assume that the response of the colonies in the colony feeding studies are due to bee bread dietary exposure alone given that these studies were designed to expose the bees to treated sugar solution and that the primary route of exposure is from consumption of the sugar solution which is supported by known consumption rates for honey bees. The Agency states in the preliminary bee risk assessment (p.48) that ingestion of pesticide residues in nectar likely represents the predominant route of exposure for bees. In addition, this is the only parameter that EPA considers the measured concentration in the hive to be the representative effects endpoint. Given that the majority of pollen and nectar residues in the registrant field residue trials were collected in the field outside of the hive with most collected directly from the flowers (a few crops had bee-collected nectar/pollen samples) a direct comparison of the exposure (outside hive) and bee bread effects (inside hive) endpoints cannot be made. Estimating bee bread concentrations from pollen and nectar residue data also poses significant problems as previously discussed.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.5 Tier II analysis for *Apis* sp. 3 270 of 412 33
EPA Statement	*Concentrations of nectar are compared directly to colony-level endpoints based on sucrose endpoints because these exposure routes are comparable. Concentrations measured in pollen are not compared directly to pollen-based endpoints for colonies, as these endpoints are not available.*

Syngenta Comments:

Syngenta's opinion is that the Agency does not need separate colony-level endpoints for pollen and for nectar in order to determine risk to bees. Separate effects endpoints and risk characterizations are not conducted for separate dietary items for other organism (e.g., insects and seeds for birds, dietary items and drinking water for humans). Dietary exposure to residues should not be solely determined by an individual source of residues on food items but by the total residue ingested, particularly for a higher-tier assessment where residue data on various food items (i.e., pollen and nectar) are available.

One simple approach to combine residue values from pollen and nectar would be to take the proportion of pollen and nectar consumed by different castes of bees (based on concentration using consumption values from the BeeREX model) and determine the total dietary exposure value for that caste. To be conservative, the total dietary exposure can be calculated based on in-hive worker bees that consume the most pollen (10% of their diet; Table 3) and nectar foragers that consume the most nectar (100% of their diet; Table 3). This range would cover the worst-case exposure scenarios for both pollen and nectar consumption and it is assumed all castes of bees that make up a functioning colony would fall between these two extremes.

Table 3. Consumption of Nectar and Pollen based on Total Percent Diet for individual Honey Bee Castes

Life stage	Caste	Average Age (days)	Nectar (mg/day)	Pollen (mg/day)	Nectar	Pollen
Adult	**Worker (cell cleaning and capping)**	**0 to 10**	**60**	**6.65**	**90%**	**10%**
	Worker (brood and queen tending)	6 to 17	140	9.6	94%	6%
	Worker (comb building, cleaning and food handling)	11 to 18	60	1.7	97%	3%
	Worker (foraging for pollen)	>18	43.5	0.041	100%	0%
	Worker (foraging for nectar)	**>18**	**292**	**0.041**	**100%**	**0%**
Larvae	Worker (winter hive maintenance)	0 to 90	29	2	94%	6%
	Drone	>10	235	0.0002	100%	0%
	Queen	0+	unknown	none		
	Worker	5	120	3.6	97%	3%
	Drone	6	130	3.6	97%	3%

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Section Title:	5.5.2 Thiamethoxam
Paragraph:	Table 5.632
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Comment No.:	34
EPA Statement	*Table 5.632. Usage data by crop group and crops for which residue data are available for foliar or soil applications of thiamethoxam. Bolded values represent major use.*

Syngenta Comments:

Table 5.632 should be labelled 5.63. In addition, foliar application residue data for apple, soybean and pumpkin have been submitted to the Agency. Additional studies to be submitted on foliar applications include blueberry and citrus. Pollen and nectar data for soil applications to strawberry have also be submitted to the Agency.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.5.2.1 Evaluation of Nectar Exposures and Colony-level Effects 1 303 of 412 35
EPA Statement	*Thiamethoxam was applied at the maximum label rate of two 0.088 lb c.e./A applications with a 5-day retreatment interval to cucumbers (MRID 49804105).*

Syngenta Comments:

Correction: Applications were made at 5-day interval up to 5 days before bloom and at the maximum application rate of 0.086 lb ai/A (not 0.088 lb c.e./A).

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.5.2.1 Evaluation of Nectar Exposures and Colony-level Effects 2 303 of 412 36
EPA Statement	*Daily averages were also higher than the thiamethoxam CFS NOAEC (25 ng c.e./g from MRID 49757201) for every site and sampling point.*

Syngenta Comments:

The Agency previously stated that "the apparent NOAEC for the thiamethoxam CFS is tentatively determined to be 32 µg c.e./L" (p. 164). Syngenta believes that the NOAEC should be 50 µg ai/L which has been confirmed with results from a second CFS conducted in 2016-2017 which included valid overwinter data.

This statement is also in the conclusions for the other crops in this section.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.5.2.1 Evaluation of Nectar Exposures and Colony-level Effects Figure 5.36 306 of 412 37
EPA Statement	*Figure 5.36. Concentrations of clothianidin equivalents in floral nectar (filled circles) and extra-floral nectar (open circles) from cotton plants treated twice (via foliar spray) with thiamethoxam at rates of 0.063 lb a.i./A (MRID 49686801). Lines represent colony level effect endpoints from the registrant-submitted clothianidin colony feeding study (CFS).*

Syngenta Comments:

The maximum value for nectar presented in Figure 5.36 does not match the data from the study (MRID 49686801). According to the study data the maximum value should be 31.5 ng c.e./g. Also from Table 1.1, the maximum concentration in nectar is listed as 9.83 ng c.e./g. In addition, the data for extra floral nectar does not match the data submitted or the results provided in Table 1.1. Finally, the conclusion that "cause of the increase in residue levels between 2013 and 2014 measurements is uncertain, but may be due to carry-over" is not supported by the data presented in Figure 5.36 which indicate that the results were similar for both years.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.5.2.1 Evaluation of Nectar Exposures and Colony-level Effects Figure 5.39 310 of 412 38
EPA Statement	*Figure 5.39. Concentrations of clothianidin equivalents in nectar from citrus treated once (via soil application) with thiamethoxam at rates ranging 0.0876-0.556 a.i./A (MRID 49881002). All values normalized to 0.172 lb a.i./A, which is the max application rate allowed for soil applications of thiamethoxam on citrus. Horizontal lines represent NOAEC (dashed) and LOAEC (solid) from registrant-submitted colony feeding study.*

Syngenta Comments:

The figure has both open and closed circles representing concentrations in nectar; however, there is no reference indicating what the open circles actually represent.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.5.2.3 Thiamethoxam Tier II Analysis (Nectar and Bee Bread) Conclusions 4 325 of 412 39
EPA Statement	*Measured residues are also available for stone fruit (peach, plum and cherry) pollen and nectar from trees treated during the previous growing season. Estimated residue levels in bee bread based on measured residues in pollen and nectar collected from stone fruit are similar to exposure levels at which colony-level effects were reported.*

Syngenta Comments:

Nectar residues detected in the stone fruit study (MRID 49819501) were below levels of concern as reported on p. 308. "Concentrations of thiamethoxam and clothianidin in nectar of stone fruit treated the previous year do not overlap with exposure levels at which effect were reported in colony feeding studies." There is uncertainty on the source of residues detected in pollen for this study given that similar concentrations were also detected in the control plots. Based on the low residues in nectar and the fact that the foliar applications were made the previous year, it is reasonable to conclude that the concentrations detected in pollen may be the result of cross contamination by bees.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.5.3 Tier II Conclusions – Synthesis 3 326 of 412 40
EPA Statement	*All of the residue data following clothianidin foliar applications provided evidence that a prebloom application interval could potentially be determined that would result in residues in pollen and nectar that would be unlikely to result in colony-level effects. However, for thiamethoxam, the general rates of decline (when observed) were much slower and would be unlikely to lead to any recommendations for pre-bloom application intervals.*

Syngenta Comments:

Syngenta disagrees with the statement that the rates of decline for thiamethoxam are much slower than clothianidin and that recommendations for pre-bloom application intervals cannot be made. Total residues of both thiamethoxam and clothianidin decline at a rapid rate after the final foliar application of thiamethoxam prior to bloom which is clearly evident in all foliar residue trials conducted. Syngenta has calculated the rates of decline expressed as SFO DT50 (total residue) to be 3.4 days for nectar for all crop studies conducted prior to 2016 including cotton (extra floral nectar) which has a very rapid rate of decline. Not including cotton (extra floral nectar), the DT50 is 7.8 days for nectar. According to the Agency's own analysis (pages 91 –

94) the mean SFO DT50s (total residue) in crop foliage for the following crops analysed also show a clear and rapid decline after application of thiamethoxam:

- Tomato = 10.1 days
- Cucumber = 2.1 days
- Cranberry = 3.3 days

Additional crop residue data have been or will be submitted to the Agency to further refine the assessment for foliar applications including data for soybean, blueberry, apple, citrus and pumpkin.

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EPA Statement	*Soil Applications* *For clothianidin soil-tested crops, data for the root and tuber and cucurbit crop groups provided evidence that a pre-bloom application interval could potentially be determined that would result in reduced residues in bee bread that would fall below those associated with colony-level effects to bees. However, all the thiamethoxam data as well as the data in the clothianidin citrus and cereal crop groups would be insufficient to determine a potential pre-bloom application interval.*

Syngenta Comments:

Additional crop residue data have been or will be submitted to the Agency to further refine the assessment for soil applications including data for tomato, cucurbits, and strawberry. In addition, other parameters besides pre-bloom application interval (e.g., soil type, rainfall, plant/crop density) appear to significantly influence the amount of residues detected in crop pollen and nectar.

Docket ID: Section Title: Paragraph: Page No.: Comment No.:	EPA-HQ-OPP-2011-0581-0034 5.7.1.3 Chronic Oral – Alfalfa Leafcutter Bee Table 5.70 335 of 412 42
EPA Statement	*Table 5.70. Summary of the maximum mean residue concentration in pollen and/or nectar from the residue studies and the chronic oral larval toxicity values for alfalfa leafcutter bees (Megachile rotundata). All values in units of ng/g-diet.*

Syngenta Comments:

The table title appears to be incorrect and indicates that the data represents larval toxicity data for alfalfa leafcutter bees rather than chronic oral adult toxicity data.